GAS-PHASE PYROLYSIS OF AMINO- AND AMIDOMETHYLIDENE MELDRUM'S ACID DERIVATIVES

BY

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In loving memory of

Herbert John Hake Warren M.B.E.,

my Grandad

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LECTURE COURSES

The following lecture courses were attended during the period of research:

Organic Research Seminars and Colloquia, Edinburgh University Chemistry Department (3 years attendance)

Current Developments in Medicinal Chemistry - Professor R. Ramage and Dr. S.L. Flitsch (10 lectures)

The Discovery of Agrochemicals - Zeneca Agrochemicals (4 lectures)

Aspects and Applications of NMR Spectroscopy - Dr. I.H. Sadler and Dr. D. Reed (4 lectures)

Synthesis of Fine Chemicals - Professor S. McKillop (East Anglia University) (4 lectures)

Current Awareness in Organic Chemistry - Dr. H. McNab, Dr. A.N. Hulme, Dr N.J. Turner, Dr. I. Gosney and Dr. R.M. Paton (5 lectures)

Patents - Protecting and Commercialising Inventions - Zeneca Specialties (4 lectures)

Royal Society of Chemistry, Perkin Division, Heterocyclic Group, Postgraduate Symposia (3 years attendance)

Concerted Cycloaddition Reactions - Dr. H. McNab (5 lectures)

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New Organic Materials for the 21st Century - Dr. G. Tennant (5 lectures)

Medicinal Chemistry - Merck, Sharp and Dohme (3 years attendance)

Pesticides - Dr. H. McNab (5 lectures)

ABSTRACT

A range of new amino- and amidomethylidene Meldrum's acid derivatives have been prepared and subjected to flash vacuum pyrolysis. The *N*-substituents were chosen as potential protecting groups for the expected pyrolysis products, pyrrol-3(2*H*)-ones. The initial use of silanes, hydrazines and benzylamines was not successful; silylamines were quantitatively deprotected on reaction with 5-methoxymethylidene Meldrum's acid (MMMA), hydrazine drivatives were successfully prepared but pyrolyses failed to produce protected pyrrolones and, although *N*-benzyl protected pyrrolones could be prepared, deprotection by hydrogenolysis did not take place at pressures up to 3 atm.

A range of amidomethylidene Meldrum's acid derivatives were prepared by two complementary routes; firstly, primary amides were reacted with MMMA to produce the desired compounds and secondly, aminomethylidene Meldrum's acid was directly acylated using acid chlorides. The second route proved to be the more efficient in terms of reaction times and yields. The formamidomethylidene derivative was studied in detail by NMR and X-ray crystallographic techniques and was shown to exist as two rotamers in both solution and solid states. All of the derivatives were successfully pyrolysed to give a general route to the parent 6*H*-1,3-oxazin-6-one and its 2-substituted derivatives (62-80%), many of which were previously unknown.

Secondary cyclic amides also successfully gave amidomethylidene derivatives on reaction with MMMA. Pyrolysis of derivatives formed from 5-membered ring amides produced new bi- and tricyclic systems including 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione. The chemistry of this system was studied in detail, and proved

to be unusual in comparison with simple pyrrolones. The compound was relatively unreactive towards electrophiles, although substitution did take place at the expected position. Conversely, it showed high reactivity towards nucleophiles though the mode of reaction depended on the nature of the nucleophile. Addition of thiophenol was shown to be completely diastereoselective by NMR studies and X-ray crystallography. Photolysis of the dione produced an unsymmetrical dimer whose structure was determined by extensive NMR studies. Methanolysis of the dione produced an *N*-unsubstituted pyrrolone, of which there are relatively few examples, and the chemistry of this compound was also investigated. Pyrolyses of derivatives produced from 6-membered ring amides were inconsistent, and produced a variety of unexpected products.

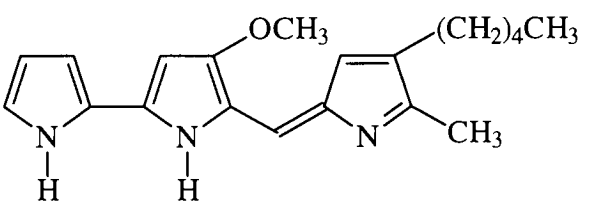
A number of thienyl analogues of the prodigiosin family of compounds were prepared. Two of the analogues prepared contained Ring C pyrroles found in naturally occurring compounds of this family, i.e., 2-methyl-3-pentylpyrrole and 2-undecylpyrrole. A new synthetic route to the former pyrrole was developed. In collaboration with Professor S. Okhuma (Japan), the analogues have been biologically tested for their inhibitory effects on proton pump activity of lysosomal $H^{\oplus}$-ATPase and the results are reported.

CONTENTS

INTRODUCTION

Preamble

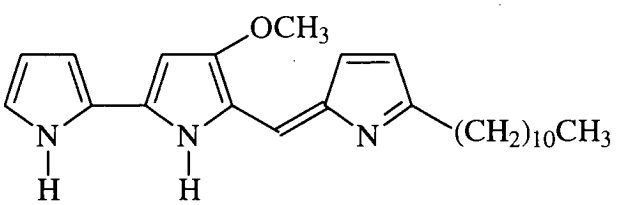
Prodigiosin **1** has made its appearance in the form of tiny blood red droplets on suitable growth media for many hundreds of years. The appearance of this red microbial growth was at first a source of superstition, often being interpreted as the blood of Christ due to its miraculous presence on consecrated bread at religious ceremonies,[1] causing proclamations of holy miracles and even inspiring riots by superstitious mobs.



Ring A Ring B Ring C

1

In more recent years, with the development of more advanced scientific techniques, prodigiosin has been isolated from a variety of micro-organisms, and from these have also been discovered many analogues of the compound. Such compounds as undecylprodigiosin **2**, metacycloprodigiosin **3** and cycloprodigiosin **4**, to name but a few, have been isolated, characterised and synthesised.



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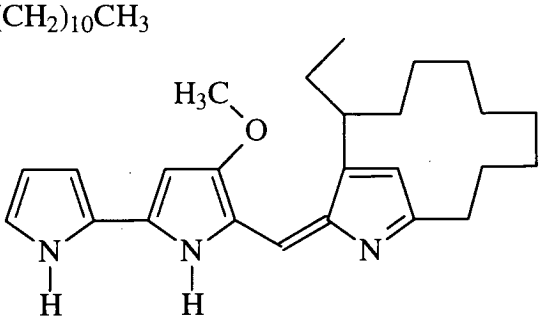

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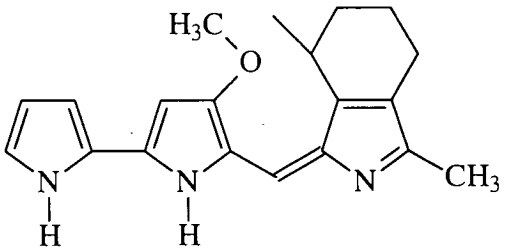
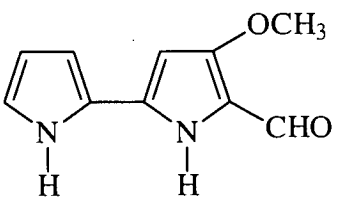


4

In these analogues, it is the right hand ring (Ring C) that changes significantly, with the core methoxybipyrrole (A-B Ring system) staying constant. Consequently, an avenue into the key intermediate **5**, the methoxybipyrrole carboxaldehyde could open the door to synthesis of this family of compounds.



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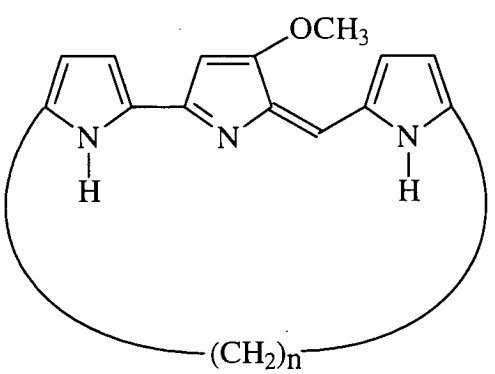
Other compounds, still of the prodigiosin family, but of a slightly different substituent pattern have also been isolated, for example the cycloalkyl prodigiosins **6**, and the tambjamines **7**.



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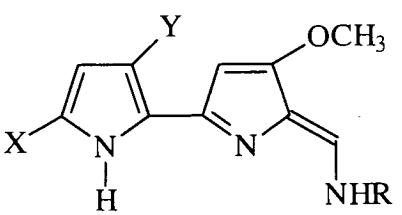
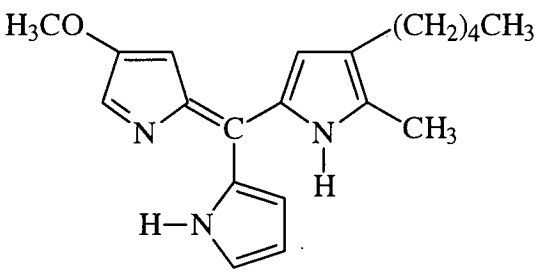


7

This introductory review presents a collation of the literature on the prodigiosin family of compounds. The compounds are dealt with in terms of isolation from natural sources and characterisation, biosynthesis, chemical synthesis, biological activity and prodigiosin analogues. Two earlier reviews in this area, by Williams and Hearn[2] and Gerber[3] have been published, but only cover publications up to 1967 and 1975 respectively. Much information has been reported in the literature since then, and consequently a more up to date review is needed.

A. ISOLATION FROM NATURAL SOURCES AND CHARACTERISATION

Bacillus prodigiosus, or *Serratia marcescens* as it is now more commonly known, is a saprophytic bacterium that occurs widely in soil and water. Prodigiosin was first isolated from this bacterium in 1929 by Wrede and Hettche[4]. Further investigations over the next five years determined the main structural features of the compound, and led to the assignment of structure **8** by Wrede and Rothhaas.[5]



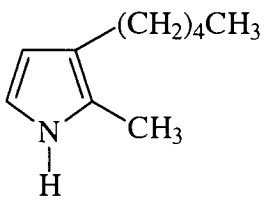
8

During the 1950's work was done to perfect isolation techniques for the pigment and to gather spectral data, in an attempt to determine/confirm the absolute structure of prodigiosin.

Work by Williams *et al* [6-8] using chromatographic methods suggested that prodigiosin previously extracted by other groups[9] may not have been a single substance, so casting doubts on the correctness of structure **8**, the tripyrrylmethene.

Studies on the absorption spectra of several synthetic tripyrrylmethenes by Treibs and Hintermeier[10] and Castro *et al* [11] concluded that comparisons with the spectrum of prodigiosin did not indicate a structure of type **8**. Around the same time, Santer and Vogel[12] isolated a compound with the formula $C_{10}H_{10}N_2O_2$ from a mutant strain of

Serratia marcescens. This was shown by biosynthetic experiments[12] and condensation with 2-methyl-3-pentylpyrrole[13] **9** to be a precursor of prodigiosin.



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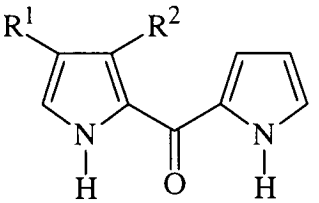
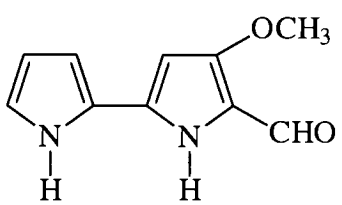


10 (**a**) $R^1 = H, R^2 = OCH_3$
(**b**) $R^1 = OCH_3, R^2 = H$

Rapoport and Holden[14] stated that for structure **8** to be correct, the compound of formula $C_{10}H_{10}N_2O_2$ must be a methoxy-2,2´-dipyrrylketone of the type **10**. Synthesis of **10a** and **10b**[14,15] and comparisons of appropriate UV absorption spectra showed the methoxydipyrrylketones to be quite different from the prodigiosin precursor isolated by Santer and Vogel.

The group concluded that the tripyrrylmethene structure **8** was untenable, and the precursor was more likely to have a 2,2´-linked pyrrole ring with possible structure **5**, giving prodigiosin itself the structure **1**. In 1962 structure **1** was confirmed by total synthesis, by Rapoport and Holden.[16]



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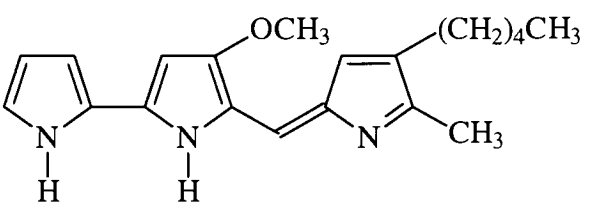
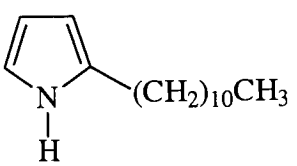


1

The discovery and characterisation of prodigiosin from strains of *Serratia marcescens* led to a detailed examination of not only this bacterium, but many others which are not members of this genus, in an attempt to isolate other compounds of this family.

Prodigiosin has subsequently been isolated from actinomycetes (from the genus *streptomyces*)[17] and a variety of types of marine bacteria such as *Pseudomonas Magnesiorubra*,[18] *Vibrio psychroerythrus*,[19] *Alteromonas rubra*,[20] *Beneckea gazogenes*[21] and *Rugamonas rubra*.[22]

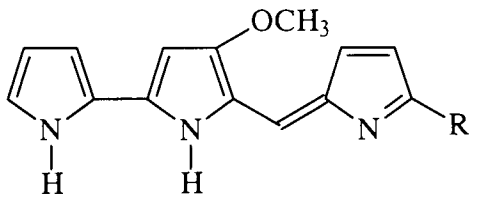
Undecylprodigiosin **2**, a C_{25} analogue of prodigiosin was isolated from *Streptomyces longisporus ruber* in the mid 1960's by two independent groups.[23-25] The presence of the undecyl side chain was indicated by mass spectra, and the structure confirmed by condensing synthetic 2-undecylpyrrole **11** with the methoxybipyrrole carboxaldehyde **5** obtained from natural sources.[23,26]



11

Actinomadura pelletieri[27] also produces undecyl prodigiosin, as well as the bacteria *Streptoverticillium rubrireticuli*[28] and *Streptomyces coelicolor*.[29]

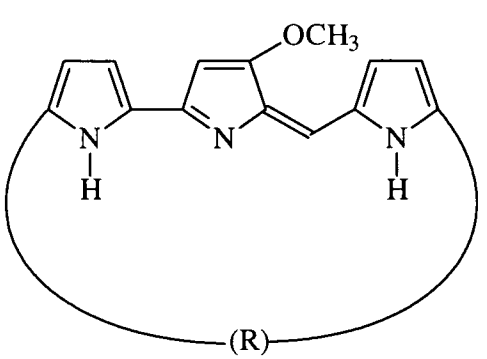
An actinomycete, *Actinomadura madurae*, was shown to produce nonylprodigiosin **12a**.[30] Gerber assigned the structure on the basis of NMR and mass spectral data.



12 (**a**) R = $(CH_2)_8CH_3$
(**b**) R = $(CH_2)_6CH_3$

A similar compound, heptylprodigiosin **12b** was identified and characterised by mass spectra from *Rugamonas rubra*,[22] a bacterial strain isolated from river water.

Further work by Gerber[31] on *Actinomadura madurae* (which had previously yielded nonylprodigiosin) resulted in the isolation of a second prodigiosin-like pigment, to which the structure **6a** was assigned.



6

(**a**) R = $(CH_2)_9$
(**b**) R = $CH(CH_3)(CH_2)_9$
(**c**) R = $CH(CH_2CH_3)(CH_2)_8$
(**d**) R = $CH(CH_3)(CH_2)_7$
(**e**) R = $(CH_2)_8CO$
(**f**) R = $CHOH(CH_2)_8$
(**g**) R = $CHOHC(X)(CH_2)_7C(Y)$
[X = O, Y = HOH or X = HOH, Y = O]

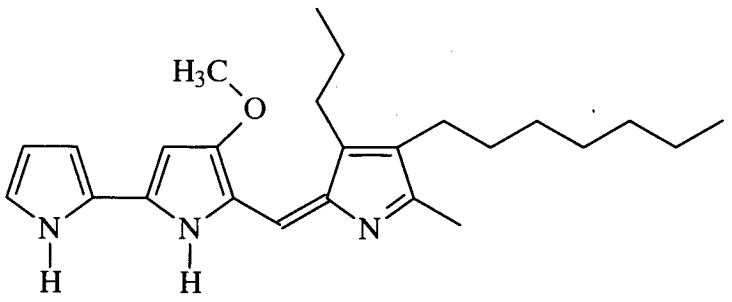
Actinomadura pelletieri produced very similar compounds **6b** and **6c**, again isolated by Gerber[27,32] and identified as methylcyclodecylprodigiosin and ethylcyclononyl-prodigiosin respectively. Four minor compounds, three containing oxygen functionalities, were also isolated and assigned the structures **6d**, **6e**, **6f** and **6g**.

Assignments of these macrocyclic type structures were based predominantly on mass spectral data obtained. The pigments were also oxidised and the acids obtained methylated and analysed by gas chromatography; this confirmed the nature of the side chains.

The positions of attachment of the side chains were made on the basis of preliminary ^{1}H NMR spectra of the pyrrole ring protons.

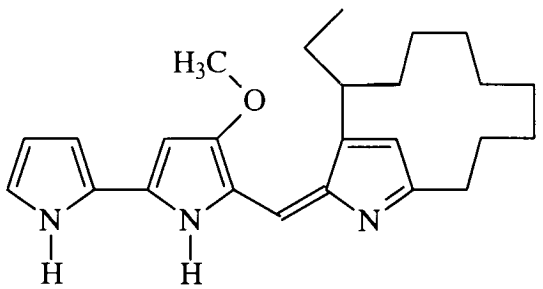
No further work has been reported in the literature to confirm the structures since these publications in the early 1970's; more detailed NMR studies are required to remove any ambiguity in Gerber's assignments.

Early work with *Streptomyces longisporus ruber* [33] isolated a new C_{25} prodigiosin-like compound; structure **13** was proposed, with propyl, heptyl and methyl groups on Ring C.



13

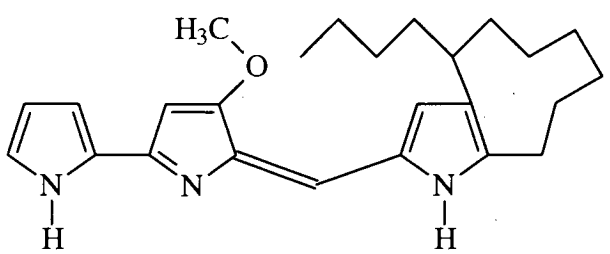
Further work on the isolated natural product,[34,35] and comparisons with a synthetically prepared sample of **13**,[36] showed the C_{25} compound to in fact have structure **3**, with pyrrole Ring C being meta-bridged.



3

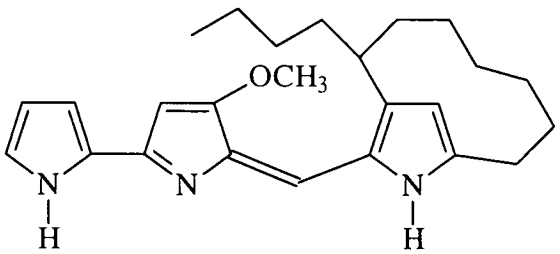
This structure was confirmed by total synthesis,[37,38] and named metacycloprodigiosin.

A similar compound was isolated from *Streptoverticillium rubrireticuli* by Gerber.[28,39] It was assigned the structure **14**, butylcycloheptylprodigiosin, with the pyrrole Ring C being ortho-bridged. The compound was subsequently isolated from *Streptomyces coelicolor*.[40]



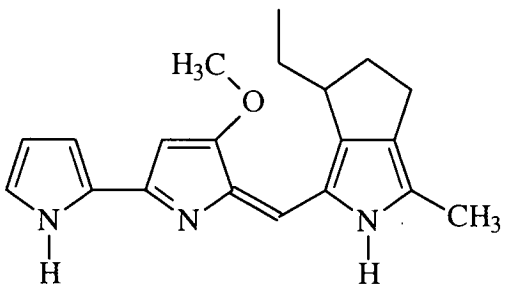
14

Further work[41,42] using extensive NMR investigations led to the conclusion that Ring C was in fact meta-bridged, giving the compound structure **15**.



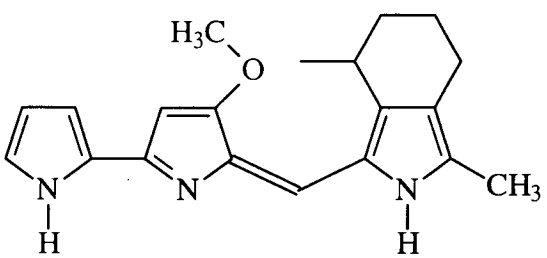
15

The marine bacterium *Alteromonas rubra*, a source of prodigiosin, produced a second prodigiosin-like compound which was isolated by Gerber and Gauthier.[20]



16

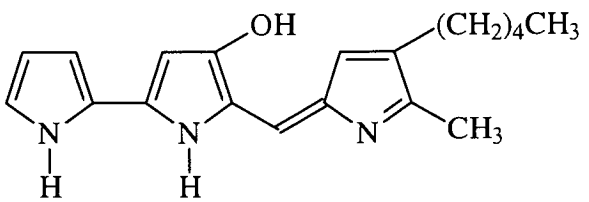
The cyclic compound was assigned structure **16** on the basis of mass spectral and NMR data. Subsequent work,[43,44] some using the higher yielding bacterium *Beneckea gazogenes* as the compound source, indicated structure **16** was slightly incorrect, the compound actually having structure **17** with a fused six (not five) membered ring and a methyl (not ethyl) substituent.



17

The compound was named cycloprodigiosin and was synthesised by Wasserman and Fukuyama in 1984.[64]

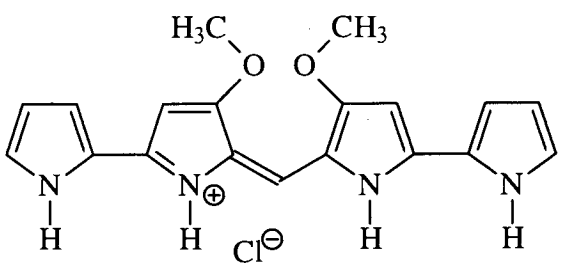
A compound of very similar structure to prodigiosin, but with a hydroxyl group in place of the methoxy group has been successfully isolated from the OF mutant of *Serratia marcescens*.[45]



18

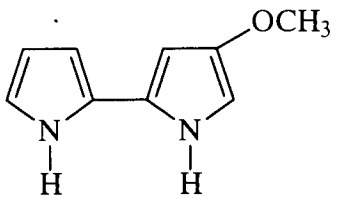
A number of attempts had been made previously[6,46] to isolate this orange pigment, norprodigiosin **18** in pure form, but all were unsuccessful. Methylation of norprodigiosin with diazomethane[45,46] successfully produced prodigiosin.

A mutant strain of *Serratia marcescens* has yielded a blue pigment which has also been shown to be a member of the prodigiosin family; Wasserman *et al*[47] isolated **19** (as the hydrochloride salt) which was shown to contain two bipyrrole residues.



19

The structure was confirmed by synthesis; condensation of methoxybipyrrole carboxaldehyde **5** with the methoxybipyrrole **20** in ethanolic HCl gave a blue pigment identical to the one isolated.

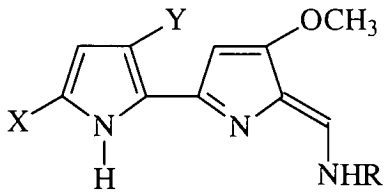


20

The same compound **19**, was later isolated from a compound ascidian[48] and a bryozoan, *Bugula dentata*.[49]

More recently, studies of certain marine animals have led to the discovery of a new class of prodigiosin-like compounds, the Tambjamines.[50,51] The compounds are present in the bryozoan *Sessibugula translucens*. These moss animals are the dietary source of two small nudibranchs, or sea slugs, *Tambje eliora* and *Tambje abdere*, which in turn are eaten by the larger, carnivorous nudibranch *Roboastra tigris*.

Four tambjamines **7a-d** were isolated from these nudibranchs and bryozoan, and characterised.[50]



7

(**a**) X = H, Y = H, R = H
(**b**) X = Br, Y = H, R = H
(**c**) X = H, Y = H, R = iso-Butyl
(**d**) X = H, Y = Br, R = iso-Butyl
(**e**) X = H, Y = H, R = CH_2CH_3
(**f**) X = H, Y = H, R = $(CH_2)_2Ph$
(**g**) X = Br, Y = H, R = CH_2CH_3
(**h**) X = Br, Y = H, R = $CH_2CH_2CH_3$
(**i**) X = Br, Y = H, R = $CH_2CH(CH_3)_2$
(**j**) X = Br, Y = H, R = $CH_2CH(CH_3)CH_2CH_3$
(**k**) X = H, Y = H, R = $(CH_2)_{11}CH_3$

The bipyrroles turn green on standing, and the colour is thought to originate from dimers of these compounds, related to the tetrapyrrole **19**.[50]

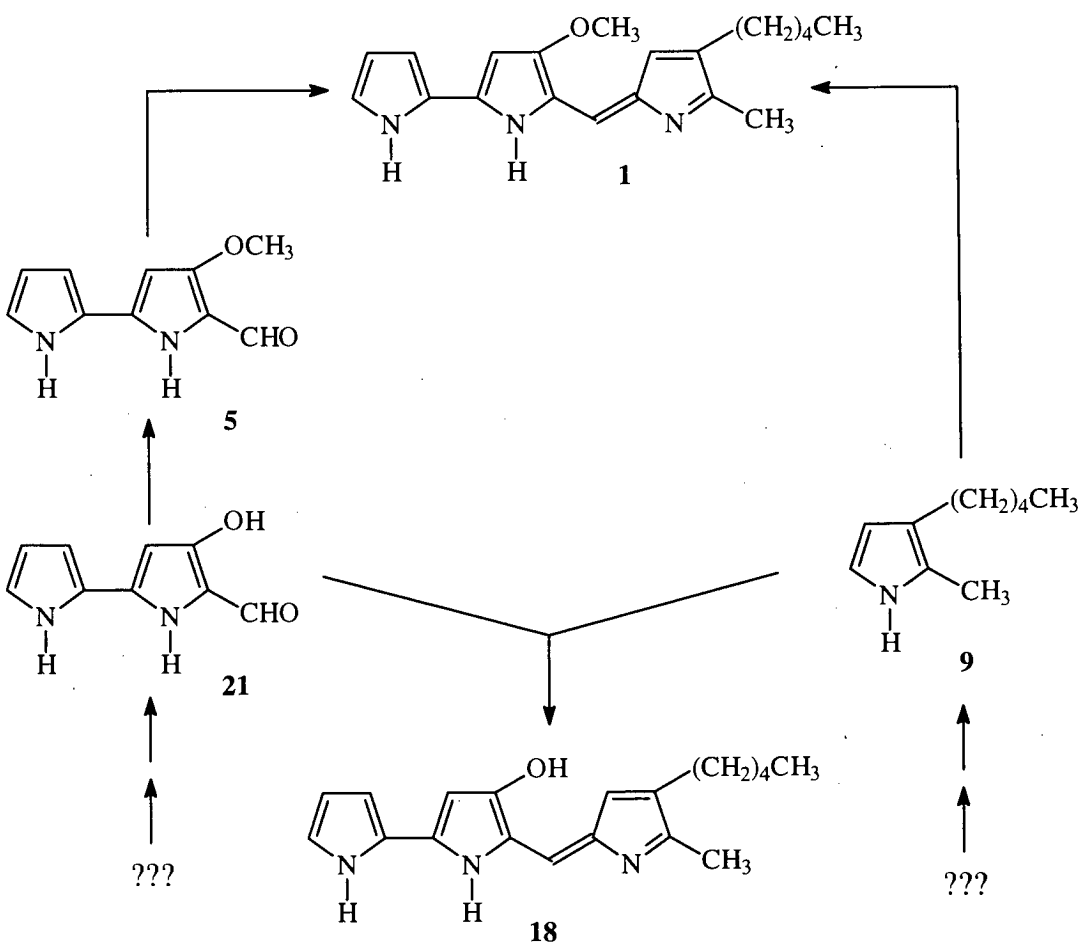
Lindquist and Fenical[51] reported the isolation of **7c** from the marine ascidian *Atapozoa* sp. (and its nudibranch grazers) as well as two new tambjamines, **7e** and **7f**. The tetrapyrrole **19** was also isolated (as the free base) from this source.

A Japanese group[52] isolated tambjamine **7k** from cultures of a *Streptomyces* species and, most recently, the bryozoan *Bugula dentata* was also found to be a source of tambjamines,[53] both known and new. Compounds **7c** and **7e** were isolated, as well as the new tambjamines **7g-j**.

B. BIOSYNTHESIS

The biosynthesis of prodigiosin and prodigiosin-like pigments has been an area of much interest since the discovery of this family of compounds.

In *Serratia marcescens*, prodigiosin **1** is derived from the coupling of aldehyde **5** with 2-methyl-3-pentylpyrrole **9**, as shown in **Scheme 1**.[2] In turn, **5** comes from the corresponding hydroxy compound **21** but the origins of **21** are as yet unknown.



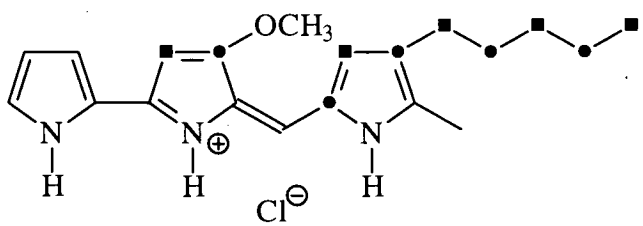
Scheme 1

Mutant strains of *Serratia marcescens* have been identified[54] in which different steps in the pathways in **Scheme 1** are blocked. For example, in some strains, all the

precursors could be made, but a defect in the enzymatic condensation of pyrrole **9** with compound **21** or compound **5** led to an absence of prodigiosin or norprodigiosin production. A block in the pathway from **21** to **5** (due to the absence of a methylating enzyme), but availability of a condensing enzyme can lead to the production of norprodigiosin **18**.

Isotopic investigations are another means of determining the biosynthetic routes to prodigiosin and its precursors **21** and **5**. Early work[9,55] reported the incorporation of acetate, proline and the nitrogen atoms of glycine into the compound. Wasserman *et al* extensively studied the incorporation patterns of ^{13}C labelled compounds into prodigiosin[56,57] and prodigiosin-like compounds,[58,59] and preliminary work in this area has also been carried out by Gerber *et al*,[41] who looked at acetate incorporation into various prodigiosin-like compounds

Initial work[56] feeding *Serratia marcescens* with [1-^{13}C]- and [2-^{13}C]-acetate showed incorporation into Ring B and Ring C of prodigiosin, as illustrated in **Scheme 2**.

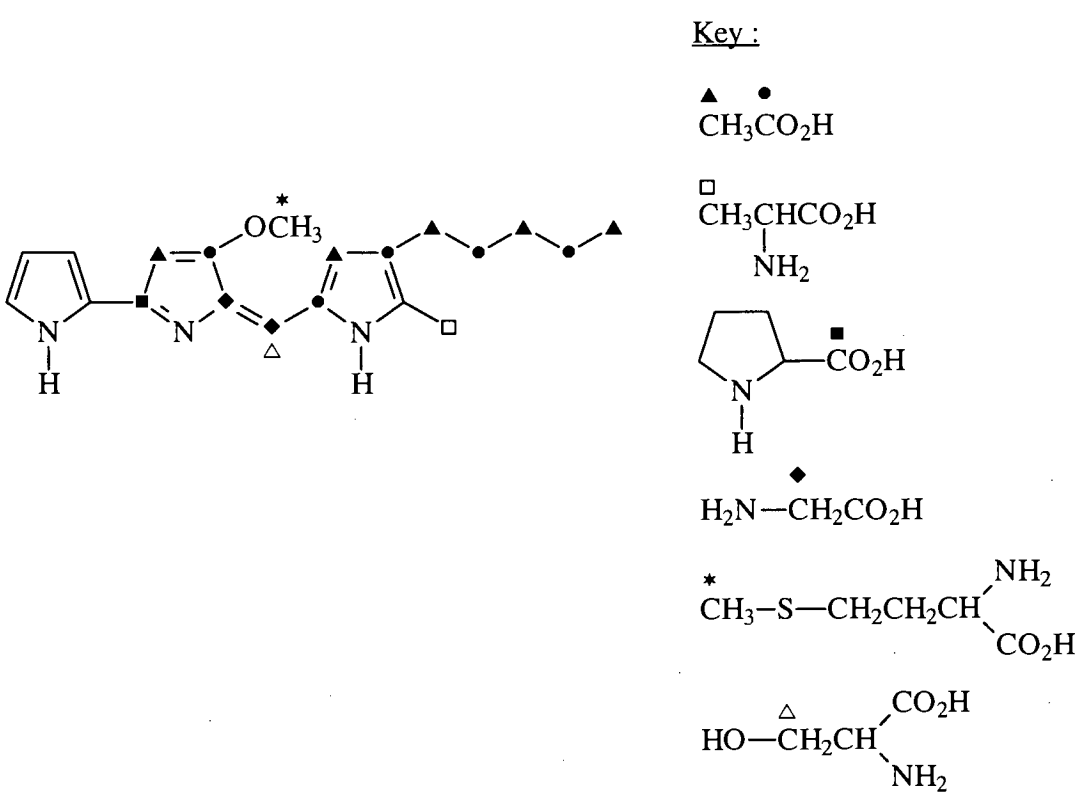


● [1-^{13}C]-acetate
■ [2-^{13}C]-acetate

Scheme 2

The pattern of primary incorporation indicated that Ring C was essentially made up from an eight-carbon polyacetate chain. Two of the carbon atoms in Ring B were derived from acetate, but no incorporation was observed in Ring A, indicating a novel route to this pyrrole ring.

As a continuation of the work[57] the bacterium was also fed with ^{13}C-labelled acetate, alanine, proline, glycine, methionine and serine and this gave a more extensive incorporation pattern, as shown in **Scheme 3**.



Scheme 3

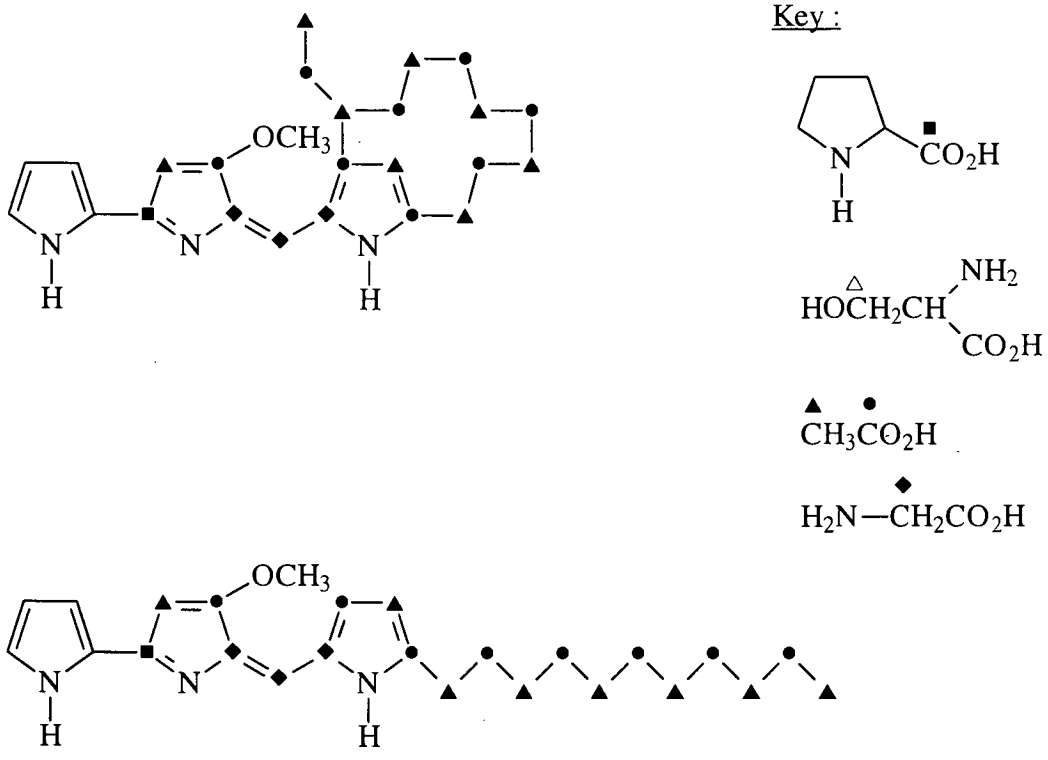
The methoxy group of prodigiosin was shown to derive from methionine and the methyl group on Ring C from the methyl group of alanine. Feeding the bacterium labelled alanine instead of acetate led to alanine incorporation at all the same sites

observed on feeding with [2-^{13}C]-acetate (as well as at the methyl carbon atom on Ring C).

There was a high specific incorporation of labelled proline into the molecule at one site only, namely the carbon atom in Ring B connected to Ring A. This provided strong support for the hypothesis that the whole of Ring A and the connecting carbon atom in Ring B were derived from a single, intact molecule of proline, or some closely related metabolite.

At the methylene carbon atom, there was a high incorporation of [2-^{13}C]-labelled glycine, as well as at the adjacent carbon atom site in Ring B. Labelled [3-^{13}C]-serine also strongly enriched the methylene carbon atom when fed, although there was no detectable enrichment of the adjacent Ring B carbon atom. Feeding experiments with [1-^{14}C]-, [2-^{14}C]- and [3-^{14}C]-serine showed that the 2-carbon atom of serine was incorporated as efficiently as the 3-carbon atom, whilst the 1-carbon atom was not incorporated. The group concluded that the methylene carbon atom and the adjacent carbon atom in Ring B of prodigiosin were derived from carbon atoms 2 and 3 of serine respectively, or from a combination of the immediate metabolic precursor of serine, i.e., glycine (as the Ring B carbon atom), and a one carbon unit source (as the methylene carbon atom).

The biosynthesis of metacycloprodigiosin and undecylprodigiosin has also been studied.[58] Samples grown from *Streptomyces longisporus ruber* were fed with labelled proline, serine, glycine and [1-^{13}C]- and [2-^{13}C]-acetate and gave the incorporation patterns shown in **Scheme 4**.



Scheme 4

The scheme shows that Ring B and the methylene carbon atom in both compounds have the same incorporation pattern as prodigiosin. In complete contrast, the carbon atom in Ring C adjacent to the methylene unit is derived from glycine in both cases, whereas in prodigiosin this atom comes from acetate.

The incorporation pattern of labelled acetate was explained by the involvement in the biosynthesis of a polyacetate chain of 14 carbon atoms. Three carbon atoms were incorporated into Ring C, and the remaining 11 into the alkyl side of the chain of undecylprodigiosin (or the meta-bridged fused ring of metacycloprodigiosin).

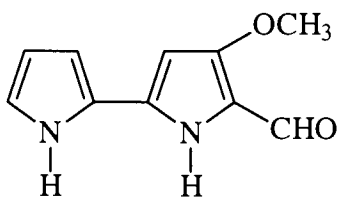
With these results in mind, Gerber *et al* [41] examined the biosynthetic incorporation of labelled acetate into nonylprodigiosin, cyclononylprodigiosin, methylcyclodecyl-

prodigiosin and butylcycloheptylprodigiosin. In all four compounds, the long alkyl chains were shown to derive from acetate units. In nonylprodigiosin and cyclononyl-prodigiosin there was some evidence for low level acetate incorporation at the 5-position of Ring A which was attributed to the proline moiety (which forms this ring) being ultimately derived from acetate.

Much has been done to elucidate the biosynthetic pathway of prodigiosin and prodigiosin-like compounds, and many questions have been answered about their ultimate biological origins.

C. CHEMICAL SYNTHESIS

As mentioned in Section A, an obvious step for formation of prodigiosin or a prodigiosin-like compound, is the coupling of methoxybipyrrole carboxaldehyde **5**, with an appropriate Ring C pyrrole. The focus of the vast majority of syntheses to emerge was therefore to find a viable synthetic route to compound **5**.

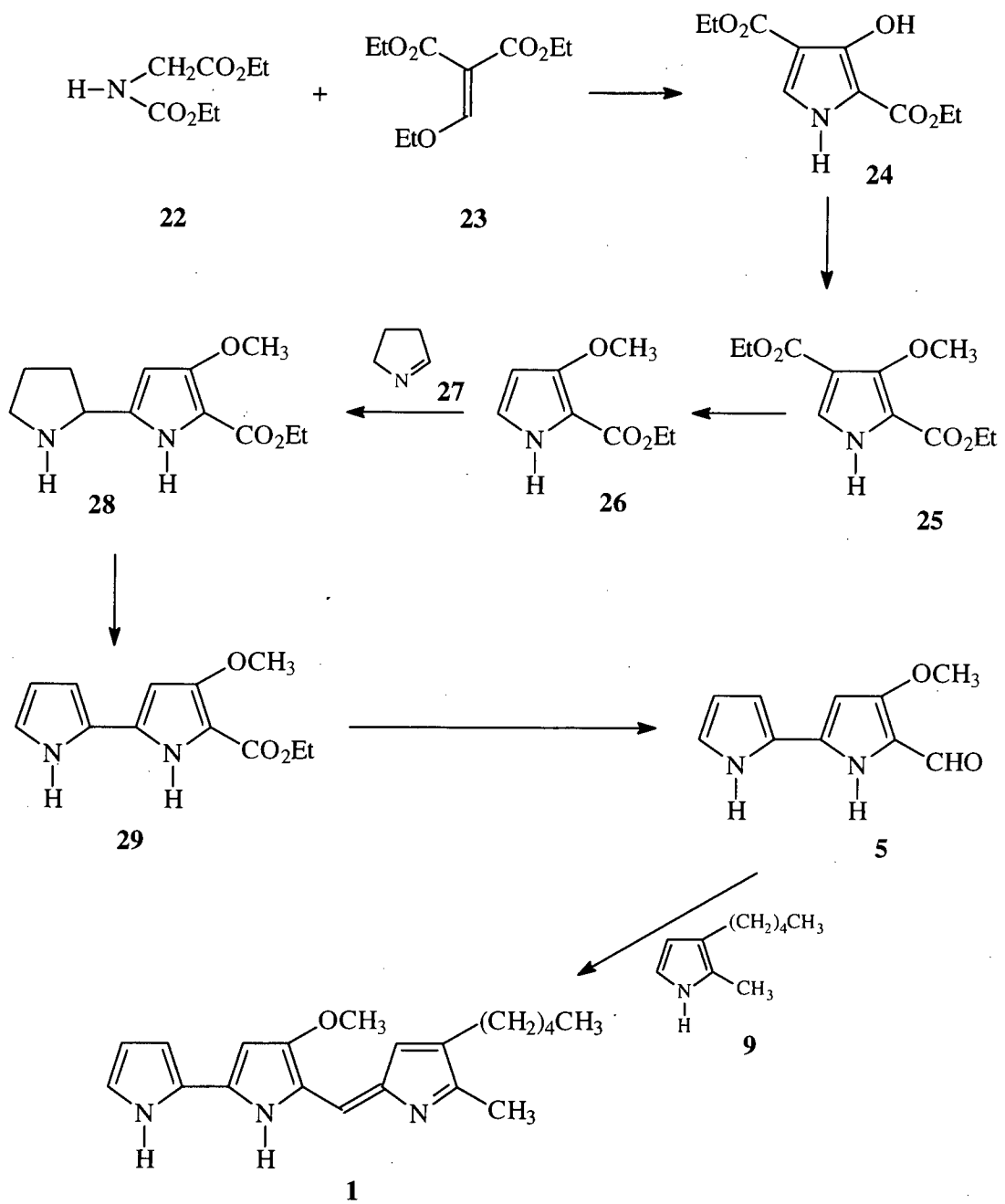


5

In 1962 Rapoport and Holden[16] produced the first synthesis of prodigiosin, enabling its structure to finally be confirmed. The approach taken is illustrated in **Scheme 5**.

Condensation of the sodium salt of ethyl-*N*-ethoxycarbonyl glycinate **22** with diethyl ethoxymethylenemalonate **23** gave the diester **24** but only in 30% crude yield. Direct treatment of the crude reaction product with diazomethane gave a mixture of compounds, which were separated by chromatography on alumina. As well as the desired product **25** (obtained in 44% yield), the *N,O*-dimethylated compound was obtained, although as a very minor component (3% yield). The third compound, produced in a yield of 35%, was monomethylated, but the methoxy group was shown to be on position C-5, as opposed to C-3 in **25**. This arose from an alternative cyclisation taking place between **22** and **23**, in which the carbanion of **22** reacted instead of the expected carbamate ion.

Treatment of compound **25** with concentrated sulfuric acid followed by an aqueous work-up hydrolysed only the β-ester, and the resulting carboxylic acid was thermally decarboxylated to give the methoxypyrrole carboxylate **26** in an overall yield for the two steps of 53%.



Scheme 5

Condensation of compound **26** with Δ^1-pyrroline **27** gave the pyrrolidinyl pyrrole **28** but in a very poor yield of only 13%. This compound was then dehydrogenated to give the bipyrrole **29** in a good yield of 82%. The ester group was converted to the aldehyde using the three-step, but low yielding (25%), McFadyen-Stevens reduction. Once this key intermediate **5** had been produced, it could be coupled with 2-methyl-3-pentylpyrrole **9** to give prodigiosin **1**. Although this synthesis of prodigiosin was ground-breaking, being the first of its kind, it was very low yielding in many steps, leaving much room for improvement.

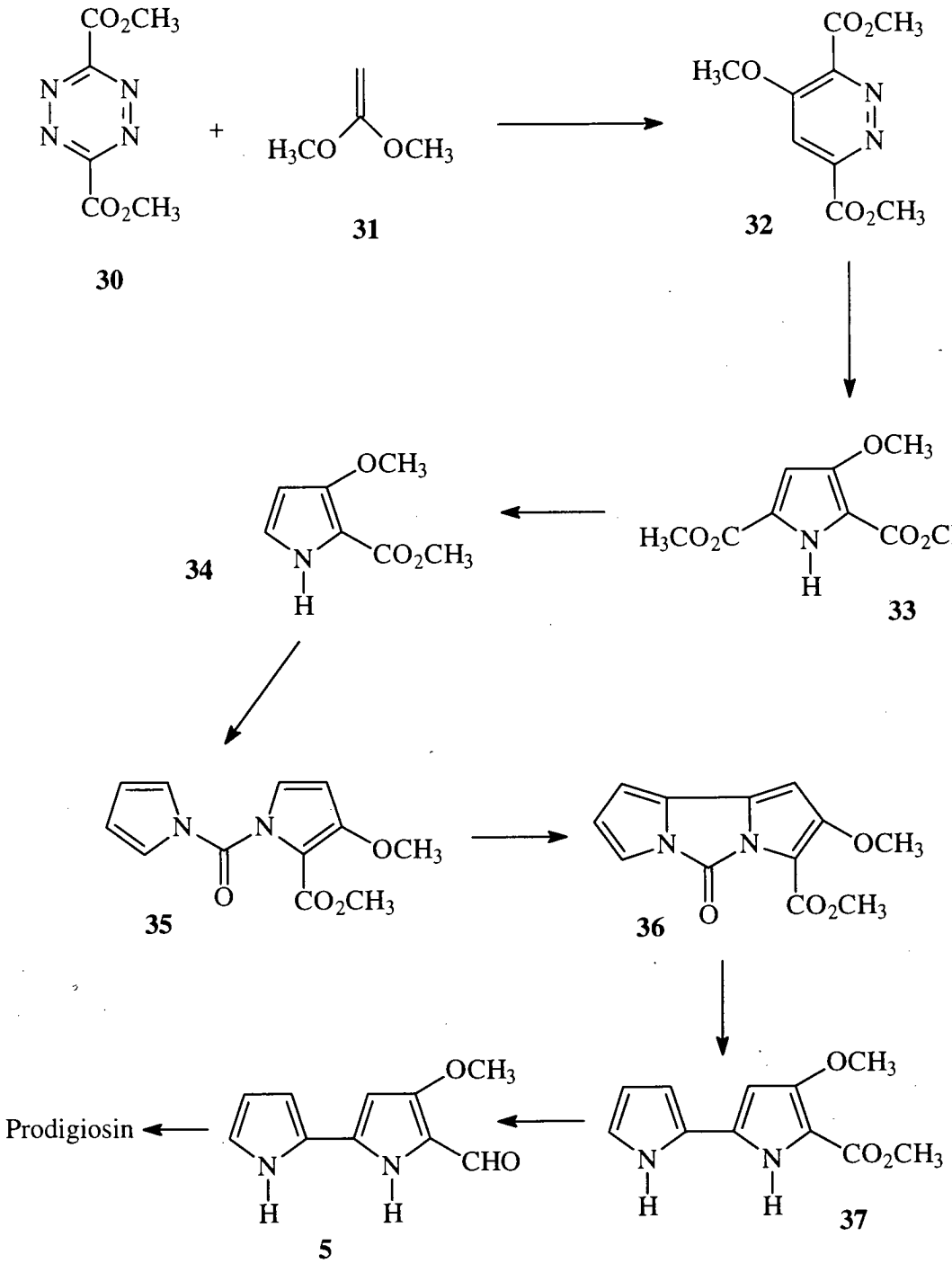
Solving the problems inherent in a synthesis including highly sensitive oxygenated pyrrole ring moieties has resulted in only two alternative syntheses of the methoxybipyrrole carboxaldehyde A-B Ring system emerging in recent years.

In the late 1980's, Boger and Patel[60,61] produced an elegant synthesis of prodigiosin, as illustrated in **Scheme 6**.

The inverse electron demand Diels-Alder reaction of the electron poor tetrazinedicarboxylate **30** with the electron rich diene 1,1-dimethoxyethene **31** produced the diazine cycloadduct **32** in almost quantitative yield. Reductive ring contraction of this adduct using zinc dust as the electron source gave the 2,3,5-trisubstituted pyrrole **33** in a yield of 68%.

A three step procedure was required to remove the carboxylate group at the 5-position. Firstly, selective hydrolysis of the electronically and sterically more accessible C-5 methoxycarbonyl group produced the carboxylic acid. Secondly, room temperature iodinative decarboxylation produced the 4,5-diiodo compound and

this could be hydrogenated over palladium on carbon as the final step to give the desired 2,3-disubstituted pyrrole **34**. Yields of all three steps were at least 89%.



Scheme 6

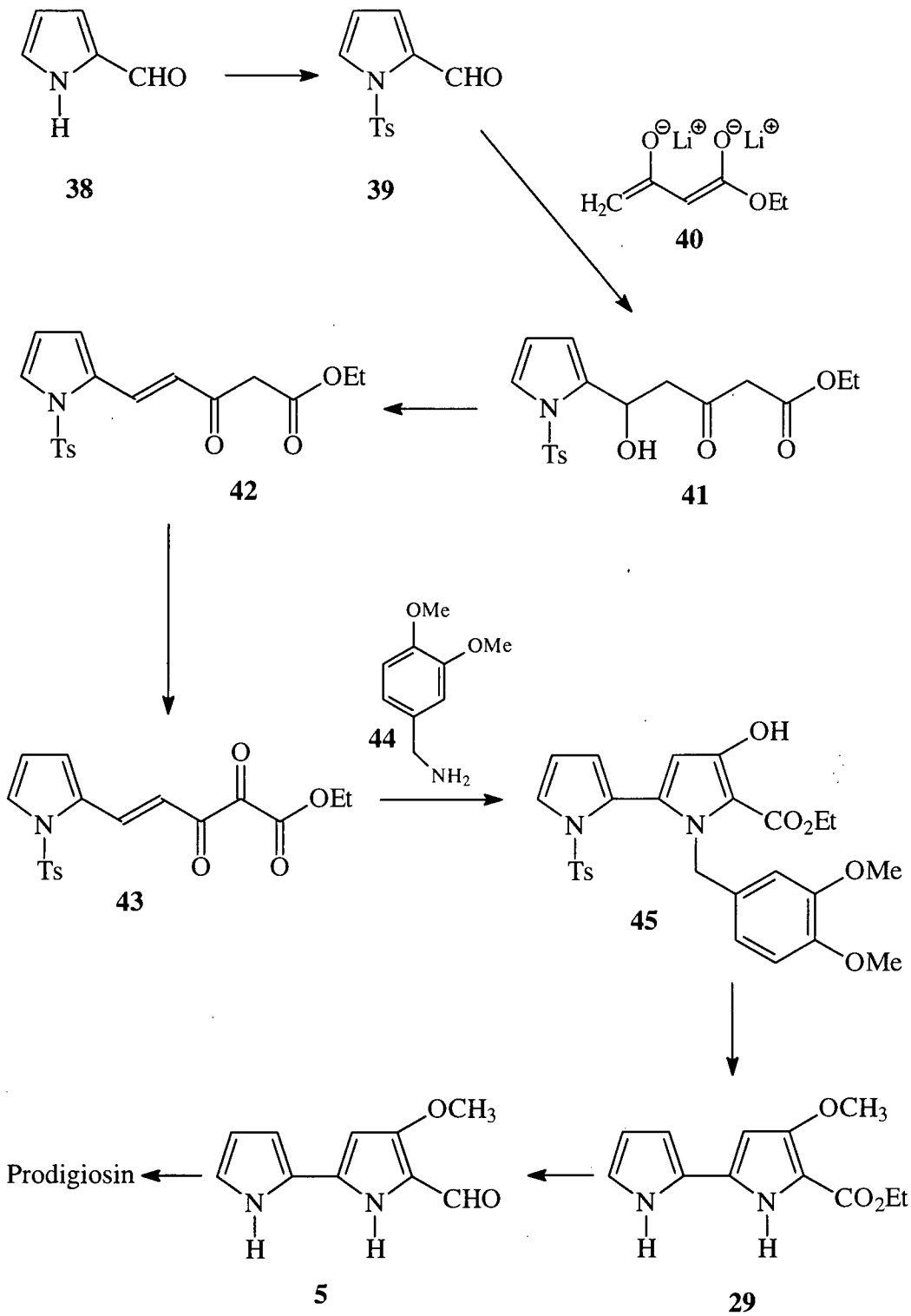
The sodium salt of the pyrrole **34** was generated and reacted with pyrrole-1-carboxylic acid (which had previously been activated by in situ acid chloride formation), producing the mixed, electron-deficient 1,1´-carbonyldipyrrole **35**. Intramolecular palladium(II) promoted bipyrrole coupling was employed to produce compound **36** in 90% yield. Polymer-supported palladium(II) acetate in acetic acid proved to be the most effective reagent for this step.

Mild methanolysis of the labile urea gave the methoxybipyrrole **37** and this was subjected to the three-step McFadyen-Stevens reduction to give the key intermediate, the methoxybipyrrole carboxaldehyde **5**, but only in a 34% yield. This could then be coupled to 2-methyl-3-pentylpyrrole to produce the synthesis target, prodigiosin.

This elegant synthesis was well designed with most steps being very high yielding, (the main exceptions being the McFadyen-Stevens reduction and the reductive ring contraction).

The third synthesis, published by Wasserman and Lombardo in 1989[62] produced a multi-step, extremely low yielding route to the methoxybipyrrole carboxaldehyde, utilising the chemistry of vicinal tricarbonyl compounds, as illustrated in **Scheme 7**.

Pyrrole-2-carboxaldehyde **38** was protected at the nitrogen atom as the tosyl compound **39**. This compound was then reacted with the dianion of ethyl acetoacetate **40** at 0°C to give the alcohol **41**. Dehydration of the alcohol with gaseous HCl gave the enone **42**.


CHO
N
H
38
CHO
N
Ts
39
O⊖Li⊕ O⊖Li⊕
H2C
OEt
40
OEt
N
Ts
OH
O
O
41
OEt
N
Ts
O
O
42
OMe
OMe
44
NH2
O
OEt
N
Ts
O
O
43
OH
CO2Et
N
N
Ts
OMe
OMe
45
OCH3
CO2Et
N
H
N
H
29
Prodigiosin
OCH3
CHO
N
H
N
H
5

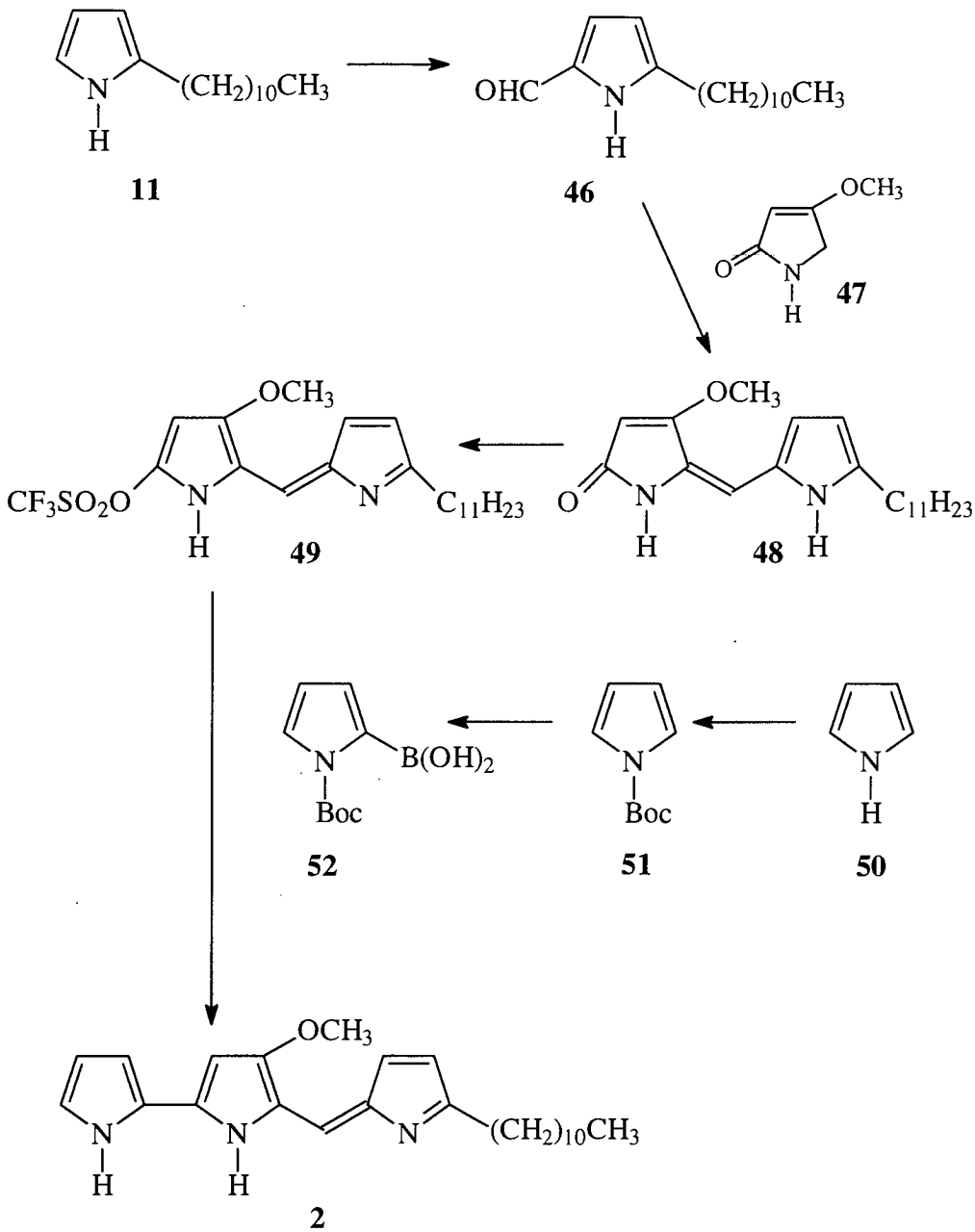
Scheme 7

The tricarbonyl compound **43** was produced by firstly condensing the active methylene group in **42** with *N,N*-dimethyl-*p*-nitrosoaniline in ethanolic sodium hydroxide. This was followed by acid hydrolysis to give **43** as a stable hydrate. Coupling with 3,4-dimethoxybenzylamine **44** in glacial acetic acid produced the bipyrrole system **45**, but the yield for this step was poor, at only 23%.

Conversion to the methoxybipyrrole **29** was achieved in three steps. Firstly, the hydroxyl group was methylated with dimethyl sulfate, then the dimethoxybenzyl group was removed using a sulfuric acid/trifluoroacetic acid mixture and finally the nitrogen atom was detosylated in ethanolic sodium hydroxide. In common with Rapoport's route in **Scheme 5** the methoxybipyrrole carboxaldehyde **5** was produced by McFadyen-Stevens reduction, but again this step was low yielding at approximately 30%. Subsequent coupling to 2-methyl-3-pentylpyrrole produced prodigiosin as the hydrobromide salt. The synthesis was extremely low yielding, with an overall yield of less than 1%.

Very recently an alternative synthesis has emerged[63] in which the B-C Ring system was prepared first, and then coupled to Ring A. The route is illustrated in **Scheme 8**, and was used to produce undecylprodigiosin.

Undecylpyrrole **11** was formylated at the 5-position under Vilsmeier conditions to give the aldehyde **46**. Condensation with the commercially available pyrrolinone **47** gave the pyrrolylmethylene compound **48** in 88% yield. This was then treated with trifluoromethanesulfonic anhydride, which gave the triflate **49** after chromatography, now suitably activated at the α-position for coupling to the pyrrole Ring A.



11 46 47 48 49 50 51 52 2

Scheme 8

Ring A was prepared from compound **50**, pyrrole. This compound was protected at the nitrogen atom with a Boc group using di-*t*-butyl dicarbonate. Compound **51** was then substituted at the 2-position with a $B(OH)_2$ group using a three step reaction with butyl lithium, trimethyl borate and hydrochloric acid, to give compound **52**.

This substituted pyrrole could then be coupled with the prepared B-C Ring system in the presence of tetrakis(triphenylphosphine)-palladium(0) and potassium carbonate to give undecylprodigiosin **2**, which was isolated as the hydrochloride salt. Boc deprotection occurred during the final step of the reaction, giving a reported overall yield of 73%, which is by far the best in the literature to the present day.

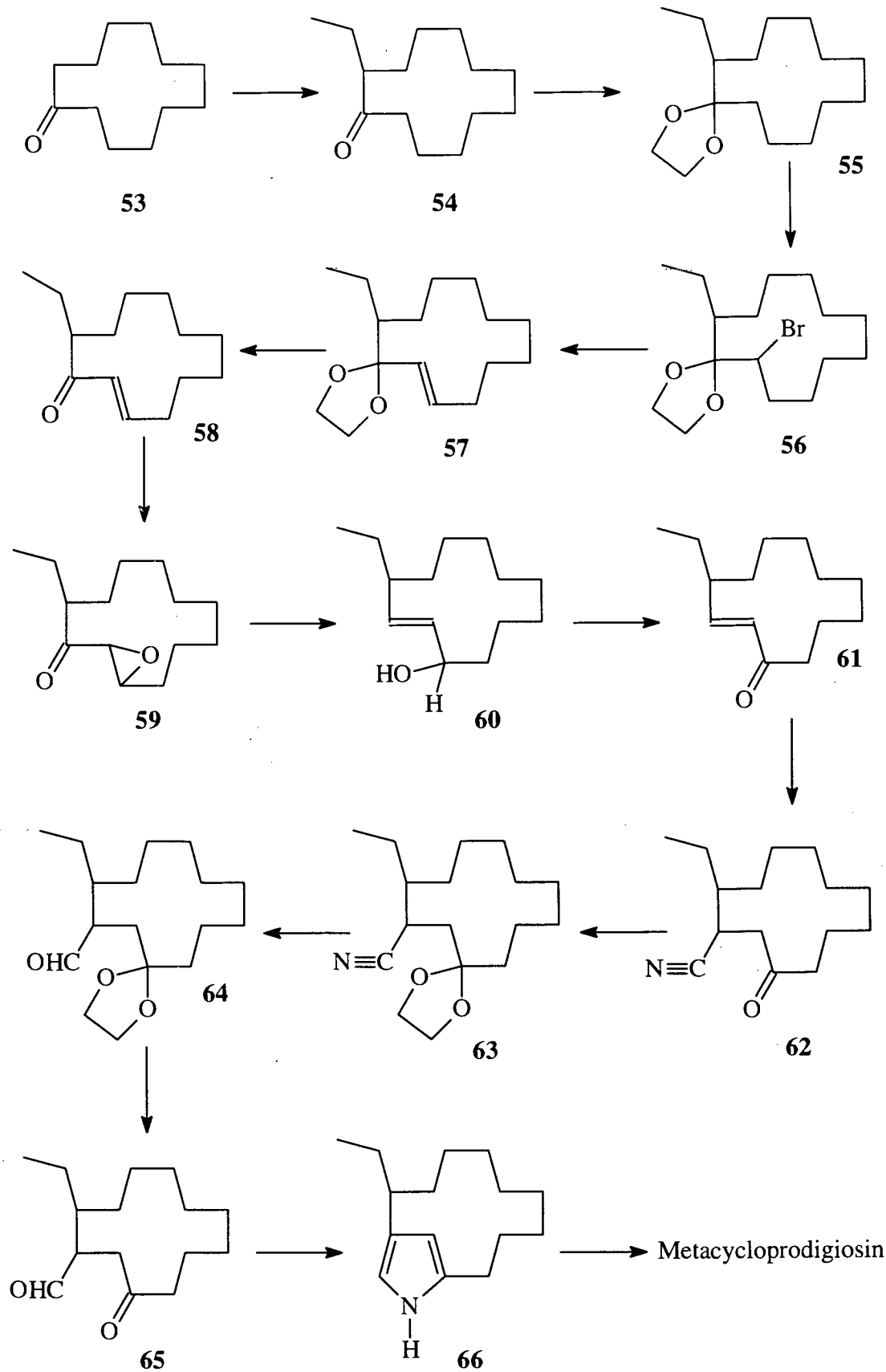
The emergence of this high yielding, elegant and, above all, concise synthesis provides a completely new route into the prodigiosin family of compounds.

Other more complex members of the prodigiosin family were also targetted for chemical synthesis, with emphasis on the construction of the required Ring C pyrrole.

Metacycloprodigiosin was synthesised by Wasserman *et al* [37] in 1969, and the route taken to produce Ring C is illustrated in **Scheme 9**.

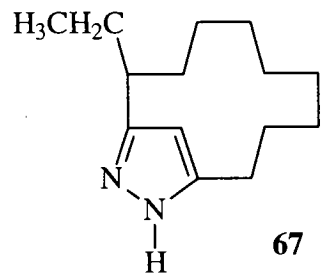
The reaction of cyclododecanone **53** with sodamide, followed by treatment of the resulting enolate anion with ethyl bromide gave a mixture which was chromatographed to give the 2-ethyl derivative **54**. Treatment of compound **54** with a mixture of ethylene glycol and *p*-toluenesulfonic acid produced the ketal **55**.

The ketal compound was brominated with pyridinium hydrobromide perbromide in almost quantitative yield to give **56**. Dehydrobromination, by heating in 1,5-diaza-bicyclo[4.3.0]non-5-ene (DBN) gave the α,β-unsaturated ethylene ketal **57**. This was then hydrolysed with aqueous acid to furnish the α,β-unsaturated ketone **58**.


53
54
55
56
57
58
59
60
61
62
63
64
65
66
Br
HO
H
OHC
N≡C
N
H
Metacycloprodigiosin

Scheme 9

Reaction of the ketone with hydrogen peroxide and sodium hydroxide gave the α.β-epoxyketone **59**. Treatment of **59** with aqueous hydrazine hydrate and a catalytic amount of acetic acid in ethanol produced the allylic alcohol **60**. A second compound was isolated from this reaction which was shown by NMR and IR to be the meta-fused pyrazole **67**, produced by an alternative reaction taking place with the hydrazine hydrate reagent.



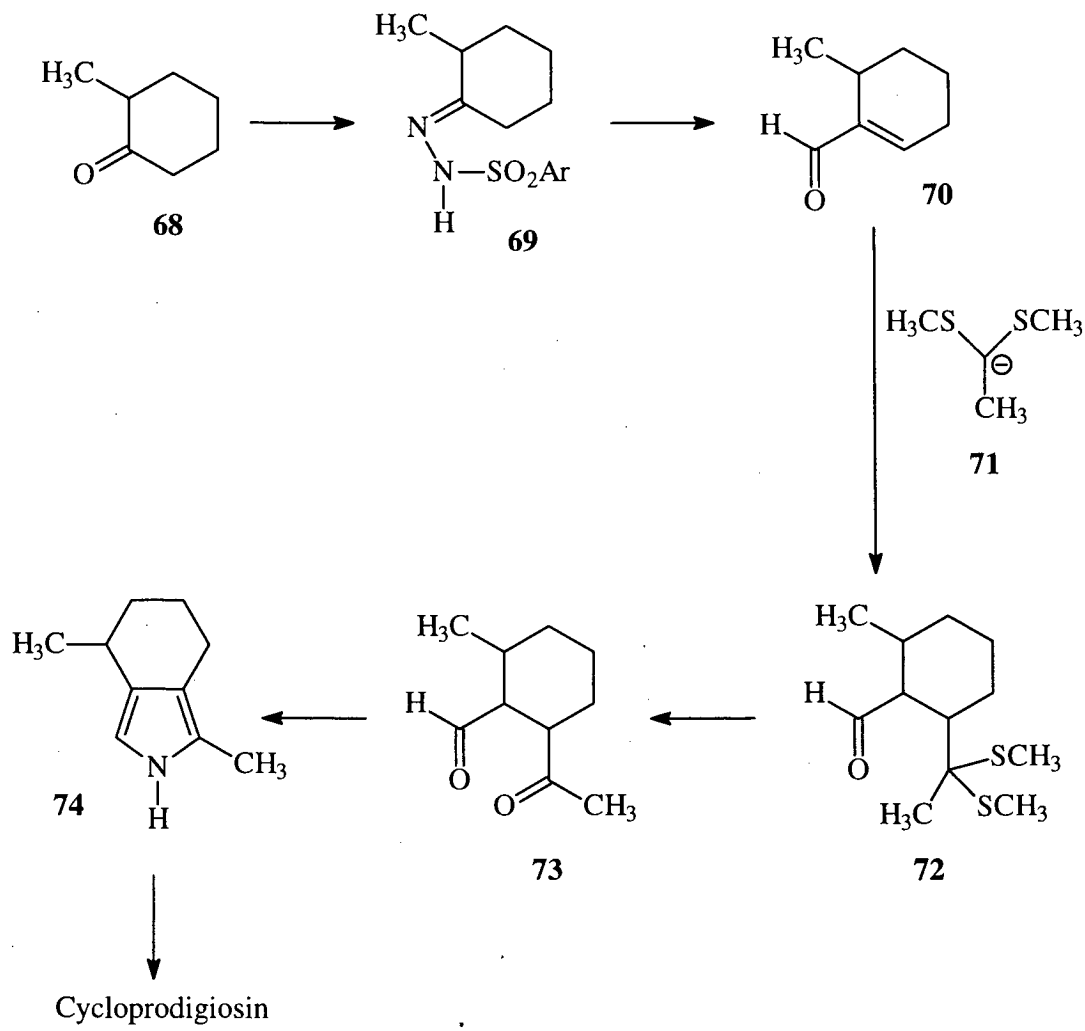
67

The desired product **60**, was oxidised with a sodium dichromate/sulfuric acid mixture to the ketone **61**. Conjugate addition of hydrogen cyanide to **61** was achieved by heating the unsaturated ketone with potassium cyanide to give **62**, but only in a moderate yield of 42%. Ketalisation, as in the conversion of compound **54** to **55** produced compound **63** and the nitrile was then reduced with diisobutylaluminium hydride (DIBAL) to give the aldehyde **64**.

In the penultimate step of Ring C formation, the ketal aldehyde was hydrolysed with aqueous acid to produce the keto-aldehyde **65**. The final step was the reaction of compound **65** with ammonium carbonate in a water/DMF mixture and the meta-fused pyrrole **66** was obtained in a 58% yield. This could then be coupled with the methoxybipyrrole carboxaldehyde **5** to give metacycloprodigiosin.

Wasserman's group was also responsible for the synthesis of cycloprodigiosin.[64] The route developed to the Ring C pyrrole needed is illustrated in **Scheme 10**.

2-Methylcyclohexanone **68** was condensed with 2,4,6-triisopropylbenzenesulfonyl hydrazide to form the hydrazone **69** in almost quantitative yield. The hydrazone was treated with two equivalents of butyl lithium which generated the vinyl anion, and this was trapped with DMF to give the α,β-unsaturated aldehyde **70**. Reaction with anion **71** produced the addition product **72**, but the yield was relatively poor at only 37%.



Scheme 10

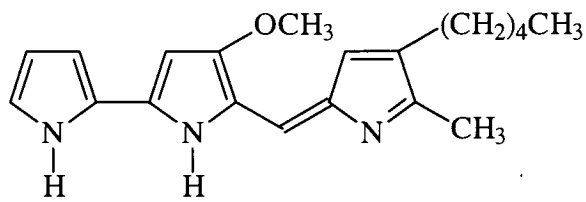
Treatment of compound **72** with mercury(II) chloride and calcium carbonate afforded the keto-aldehyde **73** and this was warmed with ammonium carbonate in a DMF/H_2O mixture to give the desired Ring C pyrrole **74**. Coupling with the methoxybipyrrole carboxaldehyde gave cycloprodigiosin as the hydrochloride salt.

The syntheses that have emerged in the literature of the past four decades have used a wide range of diverse and novel chemistry to reach their desired targets.

As yet no syntheses of cyclononylprodigiosin or methylcyclodecylprodigiosin have been published. This is also the case for the Tambjamines, although their discovery was made much more recently.

D. BIOLOGICAL ACTIVITY

Prodigiosin **1** has been reported to have various types of biological activity. Reports in the early literature, which have been reviewed[2] show the compound has antibiotic, antiprotozoal and antifungal activity. However due to many poorly controlled experiments, with essential data not reported, quantitative evaluation is difficult.



1

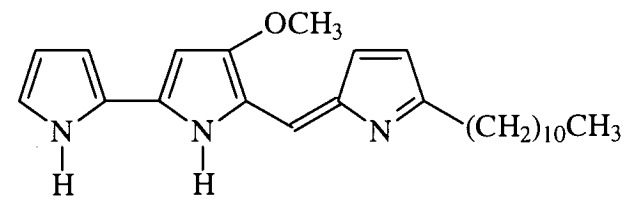
Even with these advantageous biological properties, drawbacks were noticed early on. Thus, prodigiosin was reported to have a sclerotic action,[65] rendering it clinically unusable in humans. Intramuscular injections caused marked inflammation locally, and after 3-4 intravenous injections, marked venous sclerosis.

The high toxicity of prodigiosin for rats and hamsters was also reported.[66] This, along with the low relationship between activity and toxicity was thought to be enough to preclude further studies *in vivo*.

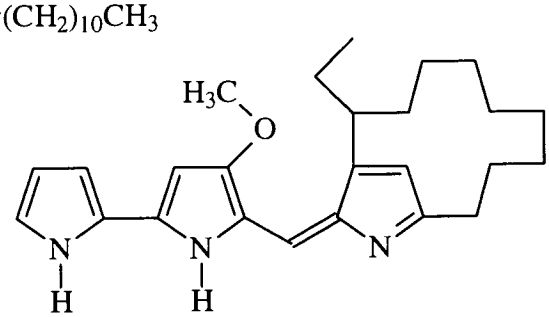
In the late 1960's Castro[67] reported on the antimalarial activity of prodigiosin. The compound showed definite activity against *Plasmodium berghei* in mice. The infected animals treated with a dose of 40 mg/kg of prodigiosin lived for approximately twice as long as those with untreated infections. However, at levels of 640 mg/kg all treated mice were dead within 5 days. As the mean survival time for

untreated mice was 6.25 days, this indicated the prodigiosin dose had reached unacceptably toxic levels.

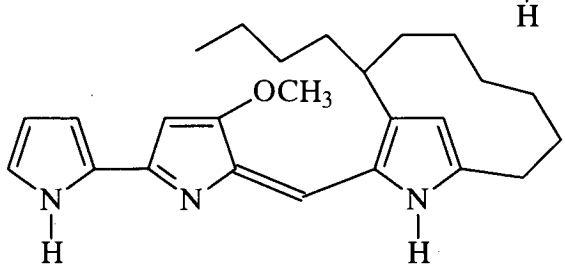
Further work was carried out almost a decade later by Gerber,[39] who studied the antimalarial activity of some of the newly discovered prodigiosin-like pigments. The activities of five compounds were reported, namely undecylprodigiosin (HCl salt) **2**, metacycloprodigiosin (HCl salt) **3**, butylcycloheptylprodigiosin (HCl salt) **15**, cyclononylprodigiosin (free base) **6a** and methylcyclodecylprodigiosin (free base) **6b**.



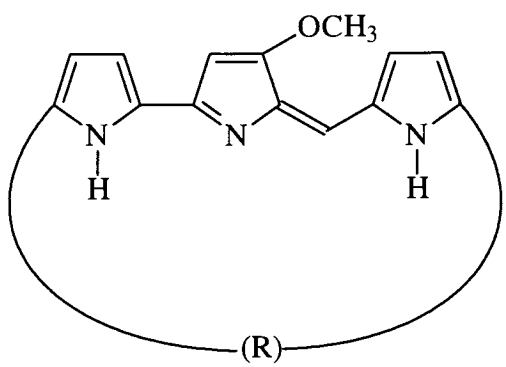
2



3



15



(**a**) R = $(CH_2)_9$

(**b**) R = $CH(CH_2)_9$ with CH_3 branch

6

Three days after infection with *Plasmodium berghei*, mice were treated with one subcutaneous administration of one of the compounds, at varying dose levels. At each dose level 5 mice were used. Without treatment, death occurred from malaria at 6-8 days. The results of two tests, A and B are summarised in **Table 1**.

Table 1

Test	Dose (mg/kg)	Increase in Mean Survival Time (Days) for Mice Treated with:				
		2	**3**	**15**	**6a**	**6b**
A	10	0.3	0.5	0.7	2.1	1.9
	20	0.5	3.9	-	3.9	2.3
	40	0.7	4.9	4.5	5.9	5.3
	80	1.1	5.9	-	8.5	6.9
	160	1.5	8.5	7.5	9	12.9
	320	-	9.3	-	0*	0*
B	10		0.5	0.5	1.9	1.7
	20		4.1	0.7	3.7	2.3
	40		5.1	4.7	6.1	5.5
	80		5.9	6.7	8.7	7.1
	160		8.5	-	-**	12.4

* All toxic deaths

** Three cured (i.e., survived 60 days) / Two toxic deaths

From the table it can be seen that all of the compounds except undecylprodigiosin **2** have a significant effect on the lifespan of the mice, even to the point of curing the malaria for **6a**, although this dose seems to be on the borderline for causing toxic death. Levels of 320 mg/kg of **6a** and **6b** caused a 100% toxic death rate, but doses one gradation lower (160 mg/kg) gave very significant increases in survival time.

Overall, the prodigiosin-like compounds examined showed promising antimalarial activity, although they were somewhat restricted by their toxicity.

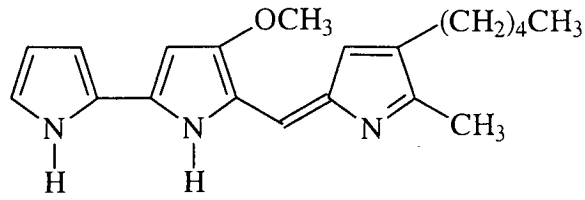
Gerber also studied the antimicrobial activity of a selection of prodigiosins.[27,68] Prodigiosin itself showed modest activity against some gram positive bacteria, actinomycetes and fungi, with minimum inhibitory concentrations of approximately 10-25 μg/ml agar. Butylcycloheptylprodigiosin, nonylprodigiosin, cyclononyl-prodigiosin and methylcyclodecylprodigiosin show similar, but weaker activity.

The antimitotic activity of prodigiosin was studied by an Italian group.[69] *Allium cepa* roots showed an inhibition of cellular division, and when exposed to high concentrations of prodigiosin showed no apical lengthening.

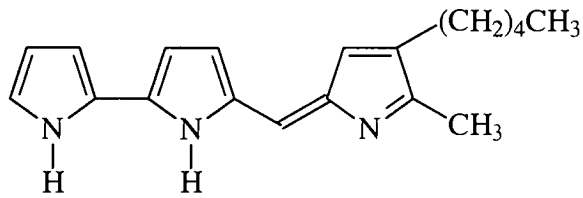
Prodigiosin is known to affect embryonic development. Kalesperis *et al* [70] reported the compound to be toxic to chick embryo development, leading to abnormal development and death. The same result was demonstrated with embryos of the American oyster, *Crassostrea virginica*.[71]

A brief Chemical Abstract[72] from Kirwin Brewery Co. Ltd stated that prodigiosin increased the survival time of mice with leukaemia by 127% when compared with untreated mice, demonstrating the compound's anticarcinogenic properties. The intravenous administrative LD_{50} was reported as 10 mg/kg.

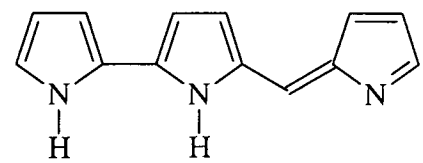
Boger and Patel[61] studied the in vitro antimicrobial and cytotoxic activity of three related compounds **1**, **75** and **76**, in an attempt to determine if the peripheral substituents in prodigiosin played a role in its activity.



1



75



76

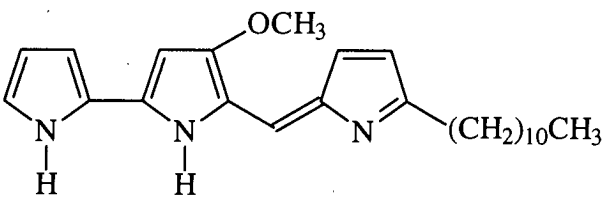
The assays were performed on a mouse melanoma, two types of mouse leukemia and a human epidermoid carcinoma of the nasopharynx. The results obtained are summarised in **Table 2**.

Table 2

Compound	*In Vitro* Cytotoxic Activity - IC_{50} (μg/ml)			
	Mouse Leukemia 1	Mouse Melanoma	Mouse Leukemia 2	Human Carcinoma
1	0.02	0.03	0.00037	0.04
75	17	6	0.07	6.4
76	12	24	0.03	0.7

As can be seen from the table, excellent activity results were obtained for prodigiosin against Mouse Leukemia 2, with an IC_{50} value of only 3.7×10^{-10} g/ml. Substantial activity was also seen in the other three tests with this compound. Compounds **75** and **76** showed much reduced cytotoxic activity, illustrating the important roles played by the substituents on prodigiosin in its biological activity, especially the methoxy group.

Recent work by a Japanese group[73] has shown undecylprodigiosin **2** to be an immunosuppressant. The compound inhibited T-lymphocyte proliferation and cytotoxic T-cell induction. This property is useful in helping to reduce the chance of rejection of transplanted organs.



2

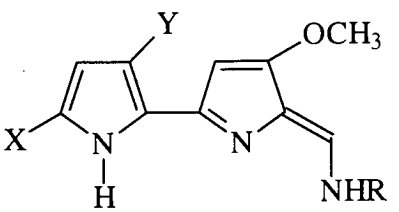
Many classic immunosuppressants also inhibit the production of leukocytes in the bone marrow, so reducing the number in the blood, which leaves the patient susceptible to infection. Contrary to other agents, undecylprodigiosin did not decrease the number of leukocytes, indicating it was an agent that specifically affected lymphocytes, a very useful biological property.

Further work[74] investigated the inhibition of vacuolar acidification, an important pathway in cells. Acidification takes place *via* the proton pump activity of vacuolar type $H^{\oplus}$-ATPase. Undecylprodigiosin was shown to be an inhibitor of this process by uncoupling vacuolar type $H^{\oplus}$-ATPase and raising pH in intact cells. The IC_{50} for the process was approximately 30 nM. Similar to other pH perturbing agents, undecylprodigiosin had very little inhibitory effect on cellular ATP levels up to concentrations of 1 μM.

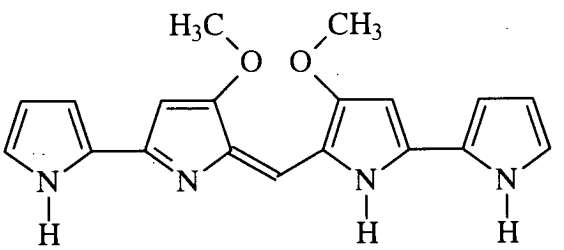
Baby hamster kidney cells treated with undecylprodigiosin (250 nM) appeared significantly dilated, with swollen mitochondria. The precise mechanism is still

uncertain but it is thought that the inhibition of the proton pump activity may trigger ionic and/or osmotic imbalances, resulting in an influx of water.

The tambjamines **7** and the tetrapyrrole **19** have a very different role to play in the nudibranchs and bryozoans from which they originate.



7



19

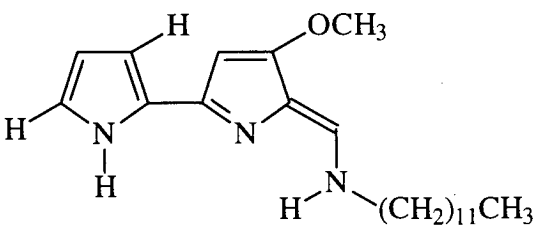
Many nudibranchs are brightly coloured, and all lack an external shell. Despite this lack of protective armour, nudibranchs are rarely eaten by predatory fish.[75] This was attributed to their cryptic colouration and habit of hiding under stones, but with further studies in this area, and the discovery of the tambjamines, it is thought that these molluscs employ some form of chemical defence mechanism.

The tambjamines in the bryozoan food source are sequestered by the grazing nudibranchs *Tambje eliora* and *Tambje abdere*. When the latter was preyed upon by the carnivorous nudibranch *Roboastra tigris* it produced a yellow mucus[76] containing

~3mg of the tambjamines, which often caused the predator to break off the attack. Under similar circumstances *Tambje eliora* attempted to swim away; it presumably contained insufficient tambjamines to deter the predator.

Both nudibranchs produced a slime trail when moving which contained low concentrations of the tambjamines. *Roboastra tigris* could follow this slime trail, using contact chemoreception to find its prey. In the same manner,[77] *Tambje eliora* was able to locate its prey *Sessibugula translucens* by detection of low levels (10^{-10}M) of tambjamines in sea water. Further up the food chain, fish were deterred from eating when their food was subjected to crude extracts of the tambjamines and tetrapyrrole,[78] the latter being the most active deterrent.

Some work has been done on the antimicrobial activity of tambjamines.[79] The tambjamines showed moderate activity against *Eschericia coli*, *Staphylococcus aureus* and *Candida albicans*. The compounds also inhibited cell division in fertilised sea urchin eggs,[79] and caused significant mortality rates in brine shrimps.[53] Specific work[80] with tambjamine **7k** showed it to inhibit the growth of human stomach cancer cell lines and mouse leukaemia cells.



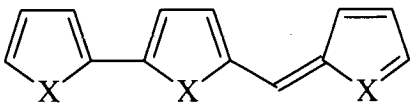
7k

Compound **7k** and the tetrapyrrole[49] **19** are also reported to show antimicrobial activity against gram-positive and gram-negative bacteria.

Prodigiosin and prodigiosin-like compounds have been shown to have many aspects of biological activity, but their high toxicity still remains a problem to be solved, perhaps by the preparation of closely related analogues.

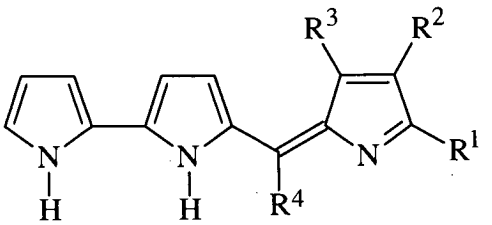
E. PRODIGIOSIN ANALOGUES

A variety of compounds have appeared in the literature that can be classed as analogues of prodigiosin, i.e. with the basic skeleton **77**.



77

When X is a nitrogen atom, and the skeleton is unsubstituted, the compound is commonly known as prodigiosene. Various substituted prodigiosenes have been prepared, for example compounds **75**, **76** and **78a-d** [81] which concentrate on different substitution patterns on the Ring C pyrrole and methylene carbon atom.



(**76**) $R^1 = R^2 = R^3 = R^4 = H$

(**78a**) $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$

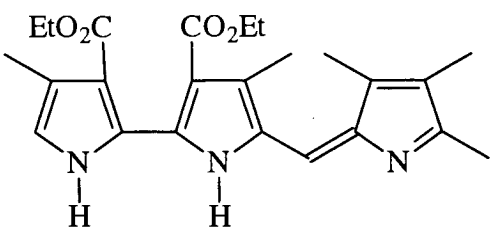
(**78b**) $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$

(**78c**) $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$

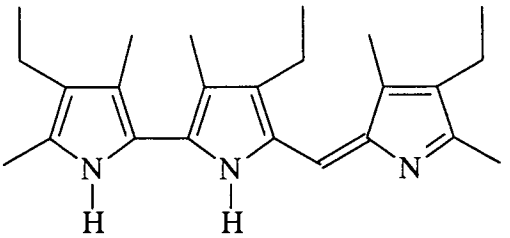
(**78d**) $R^1 = R^3 = CH_3$, $R^2 = CH_2CH_3$, $R^4 = H$

(**75**) $R^1 = CH_3$, $R^2 = (CH_2)_4CH_3$, $R^3 = R^4 = H$

More highly substituted prodigiosenes have also been prepared, such as compounds **79**[82] and **80**.[83]

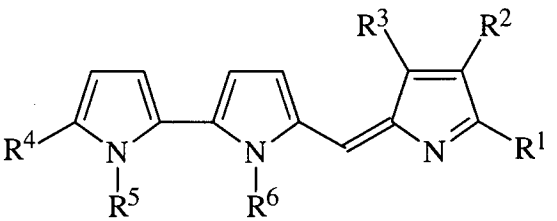


79



80

A selection of prodigiosenes have been prepared by Brown *et al* [84] in which the nitrogen atom in Ring A or Ring B is substituted, some examples of which are **81a-e**.

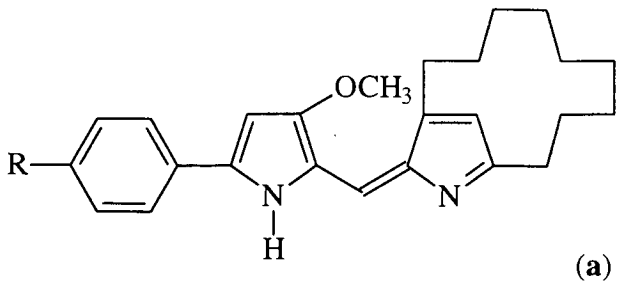


81

(**a**) $R^1 = (CH_2)_5CH_3$, $R^2 = Br$, $R^3 = R^5 = CH_3$, $R^4 = R^6 = H$
(**b**) $R^1 = R^3 = R^5 = CH_3$, $R^2 = (CH_2)_2NHCONH(CH_2)_9CH_3$, $R^4 = R^6 = H$
(**c**) $R^1 = R^3 = CH_3$, $R^2 = CH_2CH_3$, $R^5 = CH_2Ph$, $R^4 = R^6 = H$
(**d**) $R^1 = R^4 = R^5 = CH_3$, $R^2 = CO_2Et$, $R^3 = CH_2CH_2CH_3$, $R^6 = H$
(**e**) $R^1 = R^3 = R^4 = R^6 = CH_3$, $R^2 = Ph$, $R^5 = H$

Compounds have also been prepared in which the prodigiosene nucleus has been altered more significantly.

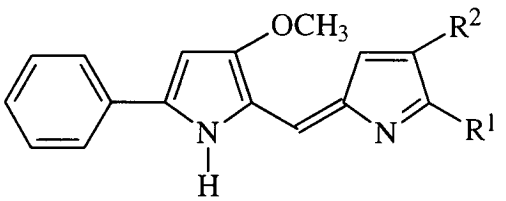
An Austrian group[85] replaced Ring A with a phenyl group and produced two analogues **82a** and **82b** similar to metacycloprodigiosin, but missing the necessary ethyl group on Ring C.



82

(**a**) R = H
(**b**) R = OH

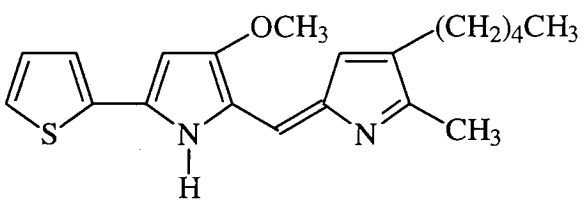
Campaigne and Shutske[86] also replaced Ring A with a phenyl group to produce compounds **83a** and **83b**. Compound **83b** retained all the other structural features associated with prodigiosin.



83

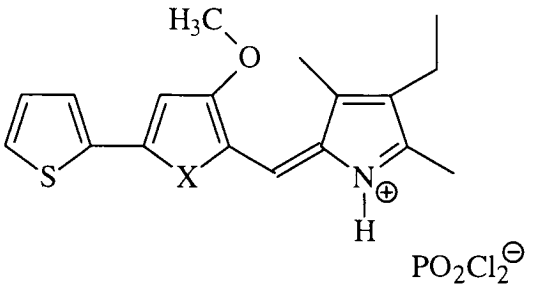
(**a**) $R^1 = R^2 = H$
(**b**) $R^1 = CH_3$, $R^2 = (CH_2)_4CH_3$

Introduction of a different heteroatom, sulfur, into Ring A produced the 2-thienyl analogue **84** which closely resembles prodigiosin itself.



84

Again working with this heteroatom, McNab *et al* [87] took the prodigiosene nucleus and introduced sulfur into one or both of the X-positions to give the prodigiosin analogues **85a** and **85b** as salts.

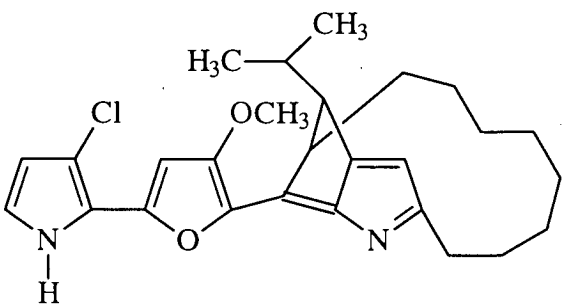


(**a**) X = S
(**b**) X = NCH_3

85

In this case the methoxy group on Ring B was retained but the Ring C substitution pattern was altered by using commercially available kryptopyrrole. Compound **85b** has the required pyrrole Ring B, but in this case the nitrogen atom was substituted.

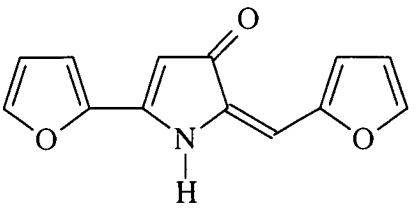
In 1992, a new antibiotic, Roseophilin was isolated from an actinomycete *Streptomyces griseoviridis*.[88] After detailed NMR studies the structure **86** was assigned which is closely related to prodigiosin in many respects.



86

The compound showed cytotoxicity against human erythroid leukaemia cells and human epidermoid carcinoma cells with IC_{50} values of 0.34 μM and 0.88 μM respectively, making it an interesting lead compound for antitumour agents.

Very recently, in 1997, a compound has been prepared by a German group[89] which is closely related in structure to the prodigiosin family.



87

Compound **87**, containing two furan rings and a central pyrrolone ring was prepared (for comparison to complex reaction products) and the structure confirmed by detailed spectroscopic work. No biological activity was reported.

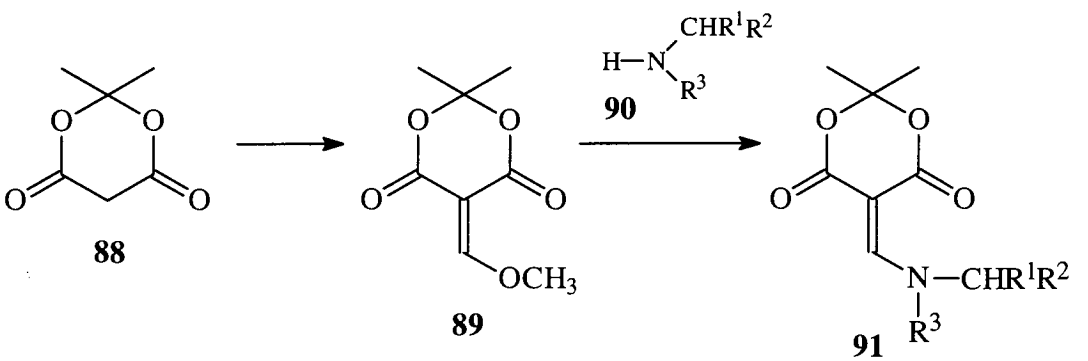
With the known problem of toxicity associated with the prodigiosin family, the area of related analogues could become much more important in future research, with many more new compounds emerging in the literature.

DISCUSSION

General Introduction

Previous work by McNab *et al*,[90] utilising the chemistry of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **88** and the technique of flash vacuum pyrolysis (FVP),[91-93] has shown its applicability to the synthesis of substituted pyrroles, and these are the key building blocks in the synthesis of prodigiosin and prodigiosin-like compounds.

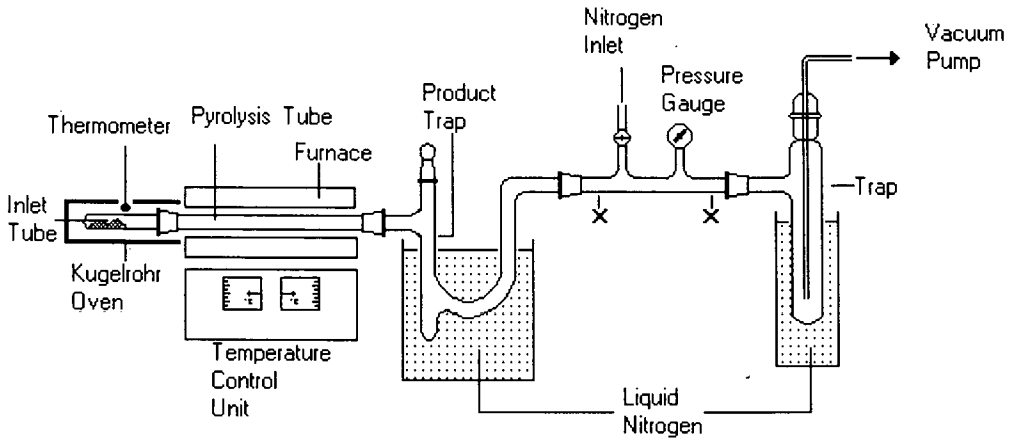
The general methodology employed is illustrated in **Scheme 11**.



Scheme 11

Reaction of Meldrum's acid **88** with trimethyl orthoformate produces 5-methoxymethylidene Meldrum's acid **89**.[94] This can then be reacted with an appropriately substituted amine, **90** to give the aminomethylidene Meldrum's acid compound **91**. A wide variety of substituted amines can be used ultimately to give a large range of substituted pyrrolones.

These aminomethylidene derivatives can then be pyrolysed, using the FVP technique. The general apparatus used for FVP is illustrated in **Scheme 12**.

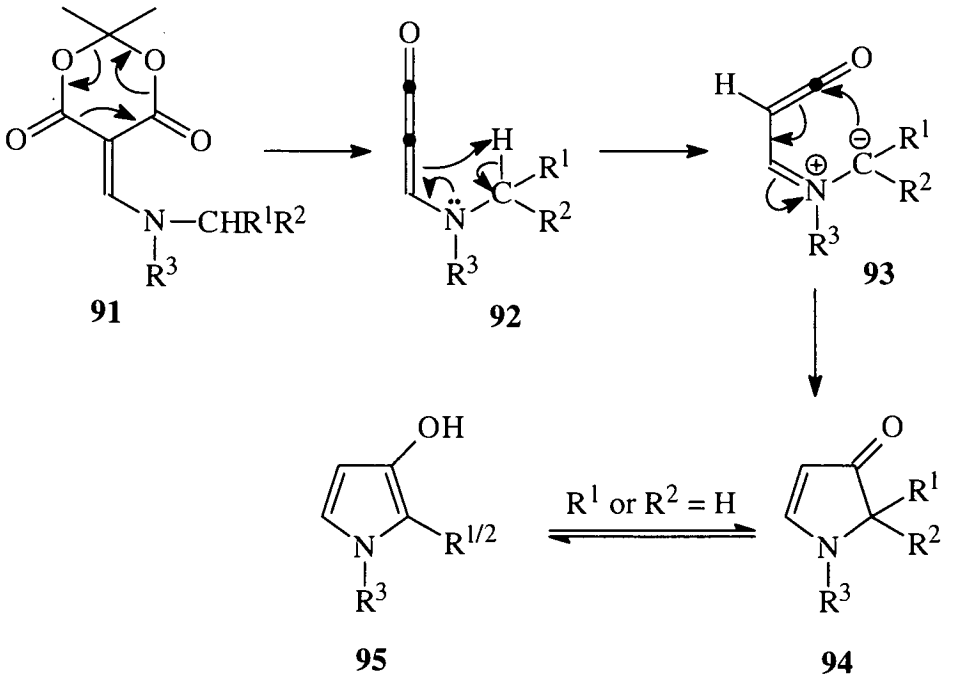


Scheme 12

The sample is volatilised from a horizontal inlet tube heated by an oven, into a silica furnace tube, which is maintained at the desired temperature by a furnace. The apparatus is kept under a vacuum of 10^{-2} to 10^{-3} Torr by the use of a rotary oil pump. Products are collected in a U-shaped trap, cooled in liquid nitrogen and situated at the exit point of the furnace.

This technique ensures that the material has a very short contact time in the hot zone (estimated to be in the order of 1-10 milliseconds). This, along with the low concentration of molecules in the hot zone, results in intramolecular, rather than intermolecular reactions occurring, although radical coupling reactions have been observed. Intramolecular gas phase reactions have many advantages over condensed phase methods, which have to occur in the presence of precursors, products and usually solvent, and this can cause many unwanted secondary reactions.

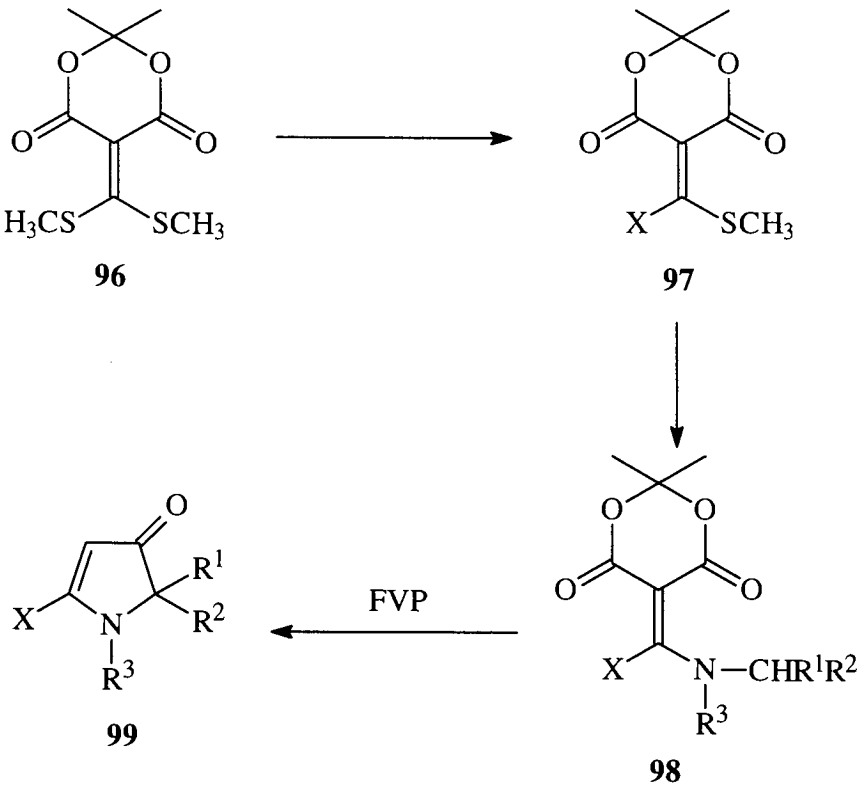
Pyrolysis of the aminomethylidene Meldrum's acid derivative **91** produces the substituted pyrrolone **94**, *via* the mechanism shown in **Scheme 13**.



Scheme 13

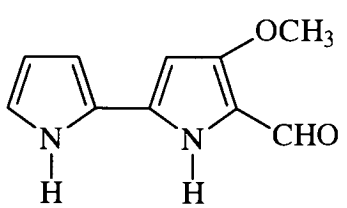
Collapse of the Meldrum's acid ring, with loss of acetone and carbon dioxide produces the methylideneketene intermediate **92**. A hydrogen shift from the site adjacent to the nitrogen atom, and cyclisation of intermediate **93** thus generated gives the *N*-substituted pyrrolone **94**. If R^1 or R^2 is a hydrogen, the compound is able to tautomerise to the hydroxypyrrole **95**. The tautomer observed is dependent on the solvent in which the compound is dissolved.[95] The hydroxy form is favoured in hydrogen bond acceptor solvents, e.g. DMSO, whereas the pyrrolone form is favoured in hydrogen bond donor solvents, e.g. methanol, or non-polar solvents e.g. chloroform.

Further substitution of the aminomethylidene compound at the methine carbon, for example compound **98**, can produce pyrrolones also substituted in the 5-position such as compound **99** after pyrolysis.



Compound **98** can be prepared from the bis(methylsulfanyl)methylidene Meldrum's acid derivative **96**.[96] Subjecting this compound to a Grignard reaction can replace just one of the SCH_3 groups to give compound **97**; the other SCH_3 group can then be replaced with an appropriately substituted amine to give compound **98**.

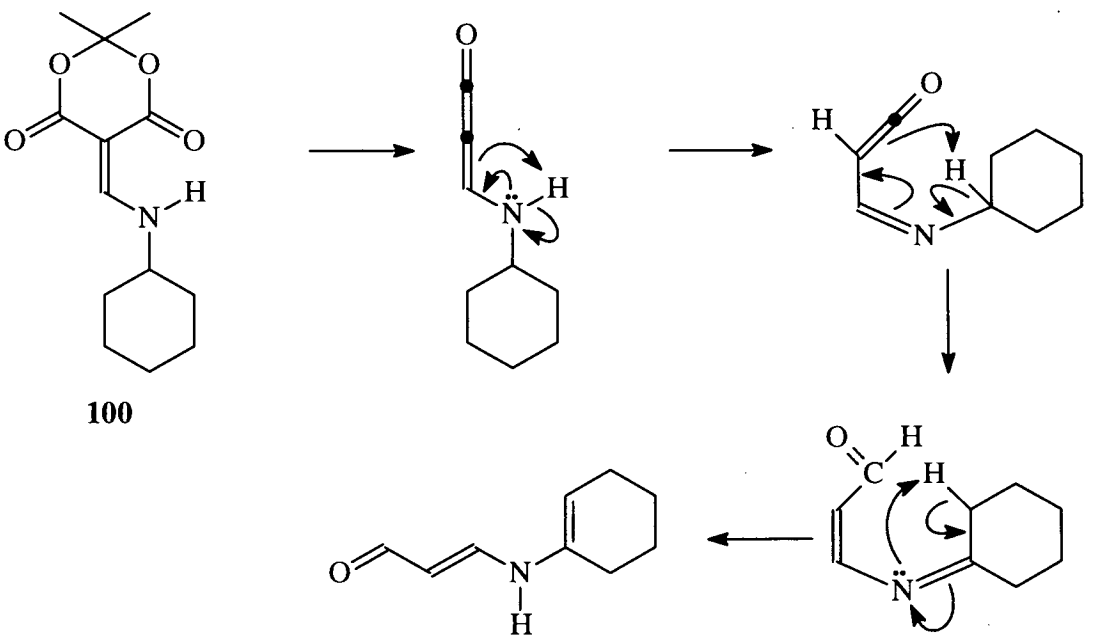
Various X substituents have been successfully incorporated into the synthesis, such as phenyl, thienyl and *p*-*t*-butylphenyl;[96] production of the methoxybipyrrole-carboxaldehyde **5** which is an intermediate in prodigiosin synthesis, would require substituent X to be a pyrrole ring and R^3 to be a hydrogen atom.



5

However, using an *N*-unsubstituted compound poses a major problem. Flash vacuum pyrolysis of derivatives containing an NH results in an alternative cyclisation to the one desired taking place. An example is illustrated in **Scheme 14**, in which pyrolysis of the cyclohexyl derivative **100**[97] results in an initial hydrogen shift of the hydrogen atom on the nitrogen atom (instead of the one from the cyclohexyl ring), and production of an enaminone system **101**.

Consequently suitable nitrogen protecting groups must be incorporated into syntheses, so cyclisation to the desired pyrrolone can occur. Any protecting group chosen must be able to survive the conditions of flash vacuum pyrolysis, without limiting the technique, for example, by lowering substrate volatility. It must also be easily removable at a later stage in the synthesis.



100

101

Scheme 14

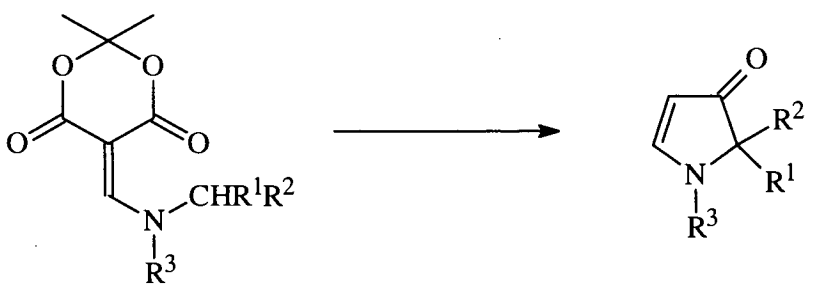
The following discussion chapters deal with the different protecting strategies employed, and the chemistry resulting from these approaches.

A. ATTEMPTS TO GENERATE *N*-PROTECTED PYRROLONES

1. Alkyl/Aryl Protecting Groups

(a) The α,α-Dimethylbenzyl Protecting Group

Previous work in this area[90,98] has shown that aminomethylidene Meldrum's acid derivatives with various alkyl and aryl substituents attached to the nitrogen atom can be prepared, for example compounds **91a-c**. All were successfully converted to their respective pyrrolones **94a-c** by FVP.

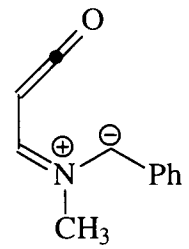


91 **94**

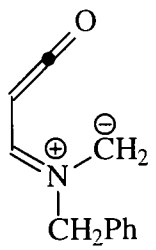
(**a**) $R^1 = H, R^2 = Ph, R^3 = CH_3$
(**b**) $R^1 = H, R^2 = H, R^3 = C(CH_3)_3$
(**c**) $R^1 = CH_3, R^2 = Ph, R^3 = CH(CH_3)Ph$

(**a**) $R^1 = H, R^2 = Ph, R^3 = CH_3$
(**b**) $R^1 = H, R^2 = H, R^3 = C(CH_3)_3$
(**c**) $R^1 = CH_3, R^2 = Ph, R^3 = CH(CH_3)Ph$

When the two substituents on the nitrogen atom are the same, as in compound **91c**, only one product is obtained regardless of which substituent is cyclised onto, due to identical FVP intermediates being formed. When the nitrogen atom substituents are different, two pyrrolone products are possible; however the two cases above, **91a** and **91b** produced pyrrolones **94a** and **94b** respectively as the only products. Using compound **91a** as the example, the two FVP intermediates that could be formed are shown as structures **102** and **103**.



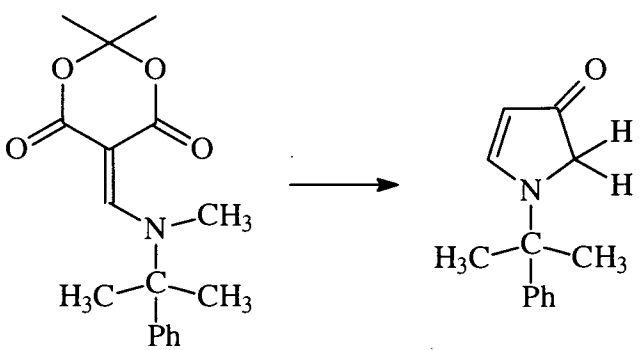
102



103

Intermediates **102** and **103** have very different stabilities; **103**, containing a primary carbanion is extremely unstable whereas **102** contains a secondary carbanion which has extra stabilisation provided by the phenyl group (into which the negative charge can be delocalised). Consequently, the 2-phenyl pyrrolone is produced exclusively, *via* intermediate **102**.

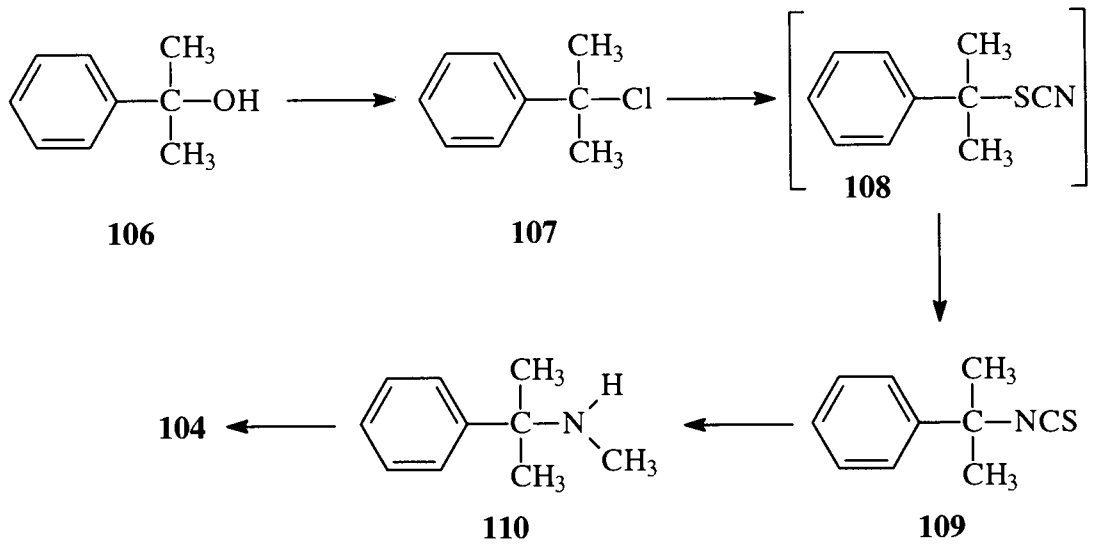
In order to produce a pyrrolone with the desired functional group on the nitrogen atom after pyrolysis, and not the 2-position, it is necessary to block the α-position of this substituent. Previous work[99] targetted the aminomethylidene derivative **104**, in which the α-positions were blocked with two methyl groups. Pyrolysis could then be expected to produce the pyrrolone **105** exclusively, with a substituent on the nitrogen atom that could potentially be cleaved at a later stage by hydrogenolysis.



104

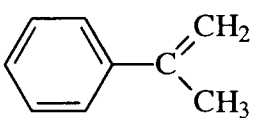
105

Preparation of compound **104** was achieved *via* the pathway shown in **Scheme 15**,[100,101] which illustrates the route taken to the required secondary amine, *N*,α,α-trimethylbenzylamine **110**.



Scheme 15

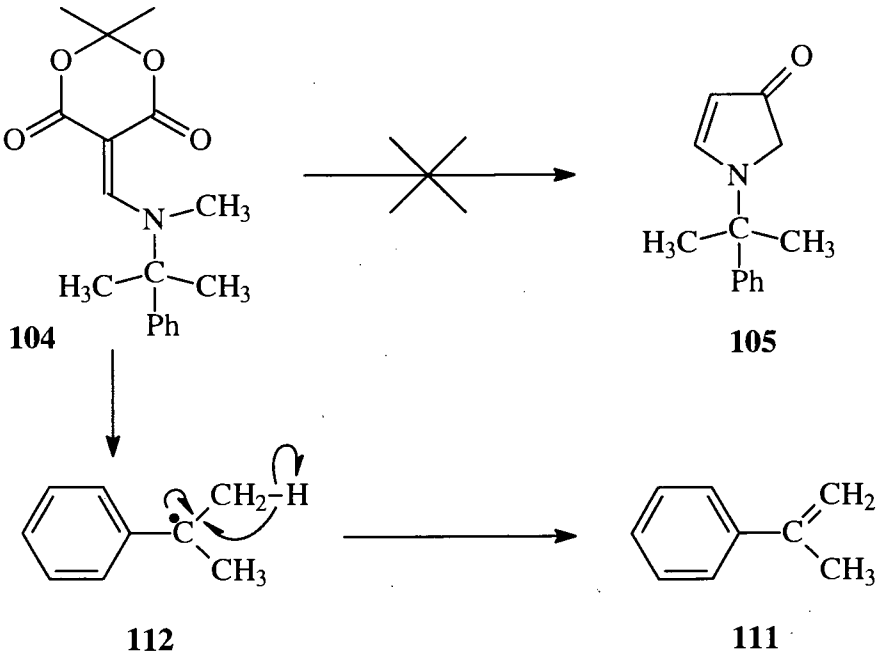
Substitution of the hydroxyl group of 2-phenylpropan-2-ol **106** using gaseous HCl produced the chlorinated compound **107**, in a moderate yield of 55%. Reaction with ammonium thiocyanate in acetone produced the thiocyanate compound **108**, which immediately isomerised to the isothiocyanate **109**. A concentrated thiocyanate solution was required for this stage; more dilute solutions, and consequently a slower rate of reaction, led to the formation of the elimination product **111**.



111

The final step to the amine **110** involved the reduction of the isothiocyanate group. This was achieved using lithium aluminium hydride to give the desired product. Reaction of the amine with 5-methoxymethylidene Meldrum's acid successfully produced the aminomethylidene Meldrum's acid derivative **104** in good yield.

Pyrolysis of this derivative would be expected to produce the *N*-substituted pyrrolone **105**. However, at a standard furnace temperature of 600 °C, the only product obtained from the pyrolysis was α-methyl styrene **111**.



Further work at different furnace temperatures, both higher and lower, failed to produce any of the desired pyrrolone. Lower temperatures gave a mixture of unreacted starting material and α-methyl styrene.

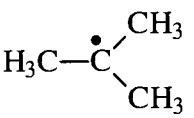
The production of α-methyl styrene was attributed to a radical cleavage of the C-N bond in the aminomethylidene derivative **104** to give the radical **112**. This stable,

tertiary radical has the advantage of being further stabilised by the adjacent phenyl group, through which the radical centre can be delocalised.

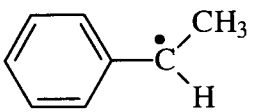
Pyrolysis of the amine **110** itself also produced α-methyl styrene **111**, although a higher furnace temperature was required for complete conversion.

As discussed earlier, work with two similarly substituted aminomethylidene Meldrum's acid compounds **91b**[90] and **91c**[98] resulted in successful production of the pyrrolones **94b** and **94c**, with no evidence of radical cleavage of the aminomethylidene derivatives during pyrolyses.

The two radicals that would have been hypothetically generated from these reactions, are **113** and **114**, and differences can be seen when compared to radical **112**.



113



114

Although radical **113** is a tertiary radical, the phenyl group which provides so much extra resonance stabilisation in **112** is absent. Radical **114** contains this phenyl group stabilisation, but is a secondary radical, which is less stable than a tertiary radical.

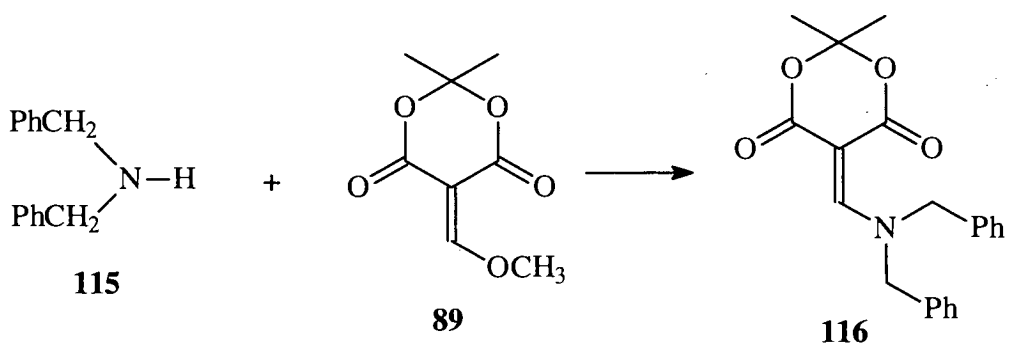
Due to this unexpected radical cleavage of the aminomethylidene Meldrum's acid derivative **104** to give α-methylstyrene instead of the desired *N*-protected pyrrolone this line of investigation was not continued and another protecting group strategy was sought.

(b) The Benzyl Group

A potential nitrogen atom protecting group for pyrrolones is the benzyl group, which is known to pyrolyse successfully[90] and can potentially be cleaved by a variety of methods, making it an attractive substituent. The unique *N*-unsubstituted pyrrolone product ultimately produced could then be studied in terms of, for example, electrophilic substitution and *O* vs *C* vs *N* alkylation to name but two areas, to give valuable insights into the chemistry of these type of compounds, which are integral parts of the prodigiosin family of compounds.

In order to produce an *N*-benzylated pyrrolone it was necessary to use the dibenzylated aminomethylidene Meldrum's acid derivative **116**.[90] As explained earlier, mono *N*-benzylated derivatives produce 2-phenyl substituted pyrrolones due to the stability of the particular FVP intermediates found.

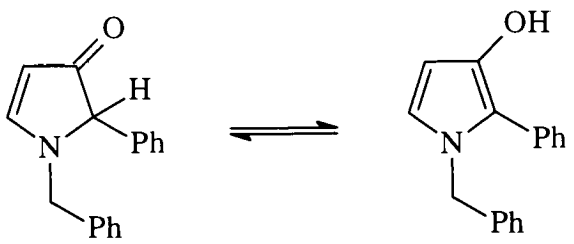
The required derivative was prepared from *N*,*N*-dibenzylamine **115** and 5-methoxymethylidene Meldrum's acid **89**.



115 **89** **116**

Reactions between 5-methoxymethylidene Meldrum's acid and primary and secondary amines are facile, and after a 5 min reaction at room temperature in acetonitrile, compound **116** was obtained in a yield in excess of 90%.

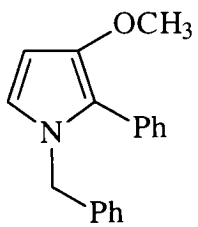
Compound **116** was then pyrolysed at 600 °C to give the pyrrolone product (**117** in a yield of 63%) as a mixture of tautomers (in $CDCl_3$), i.e., both the keto **117** and the enol **118** forms were present.



117 **118**

In the keto form, the CH_2 hydrogen atoms of the benzyl group gave rise to separate signals in the ^1H NMR spectrum, showing them to be diastereotopic. As expected in the enol form, these protons were equivalent, giving a single peak with an integral equivalent to two protons.

Finally the pyrrolone was *O*-methylated, using the standard conditions[102] of sodium hydride and methyl *p*-toluenesulfonate in 1,3-dimethyl-2-imidazolidinone, to produce *N*-benzyl-3-methoxy-2-phenylpyrrole **119** in a moderate yield of 41%.



119

With the required starting material synthesised, the cleavage of the *N*-benzyl group could be studied.

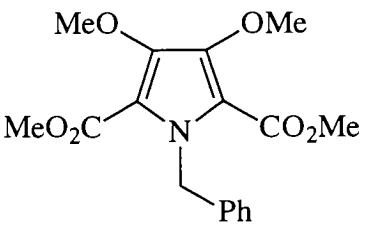
Various methods are available for removal of an *N*-benzyl group. For example, sodium in liquid ammonia has been reported to give excellent yields of deprotected products,[103] but these strongly reducing conditions may not be compatible with the methoxypyrrole moiety. More recently, catalytic transfer hydrogenation utilising formic acid as the hydrogen donor was reported as a method of debenzylation.[104]

Many reports have appeared in the literature in which hydrogenation has been used as a method of removing an *N*-benzyl group.[105] Palladium is reported to be the preferred catalyst, with alcohols or acetic acid as the preferred hydrogenation solvents. A publication in 1988[106] described a method for hydrogenolysis of *N*-benzylamines using $Pd(OH)_2$, better known as Pearlman's catalyst[107] using extremely mild conditions. Hydrogenation has been shown to be widely applicable and was the preferred method for the attempted deprotection of the *N*-benzyl substituted methoxypyrrole.

Room temperature hydrogenation of **119** over 5% palladium on carbon, using ethanol as solvent, and a pressure of 45 p.s.i. (~3 atm) gave a quantitative recovery of starting material after a 3.5 h reaction. Using glacial acetic acid as the hydrogenation solvent, with a basic work-up, again gave only starting material, with no evidence of the debenzylated product.

Hydrogenation of the methoxypyrrole **119** with Pearlman's catalyst, reported as an alternative where other palladium catalysts have failed,[105] with methanol as solvent and a pressure of 45 p.s.i. (~3 atm) again resulted in recovery of only unreacted starting material. Using glacial acetic acid as the reaction solvent had no effect, nor did extending the hydrogenation time to 24 h.

A recent publication[108] from a German group reported the debenzylation of the substituted pyrrole **120**.



120

Cleavage of the nitrogen atom protecting group was achieved by hydrogenation over 10% palladium on carbon in glacial acetic acid, but a pressure of 20 atm was required for 24 h for a successful reaction.

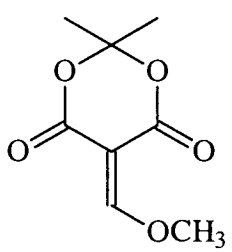
As this strategy was designed to study the chemistry of *N*-unsubstituted pyrrolones rather than to provide a rapid route into the prodigiosin family of compounds, and had proved unsuccessful, it was not pursued. Future work in this area could be to study the debenzylation of compound **119** using high pressure hydrogenation, or other chemical methods.

2. The Silyl Protecting Group

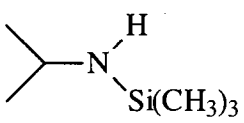
The use of organosilicon reagents as protective groups in organic synthesis[109] has developed rapidly since the early 1970's when silyl ethers were introduced for the protection of hydroxyl groups. Work initially focused on protection of the oxygen atom in its various guises, but has been extended to other atoms such as nitrogen, sulfur and phosphorus, as well as carbon.

A range of silicon protecting groups have emerged in the literature, such as trimethylsilyl (TMS) and *t*-butyldimethylsilyl (TBDMS) to name but two of the most commonly used, and their use for protection of oxygen functionalities has expanded rapidly. However, protection of nitrogen functionalities has met with less success; many *N*-silyl derivatives have proved highly sensitive to moisture and so are readily cleaved by hydrolysis.[110] Colvin[111] also reported aminosilanes to be the most reactive class of organosilanes after halogenosilanes (in which silicon is bonded to a more electronegative element) resulting in a readily cleaved N-Si bond, and even making some of these compounds potent silyl-transfer reagents.

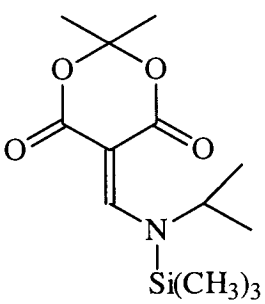
Previous preliminary work[112] utilising silyl-protected amines involved the reaction of 5-methoxymethylidene Meldrum's acid **89** with the protected amine **121**.



89

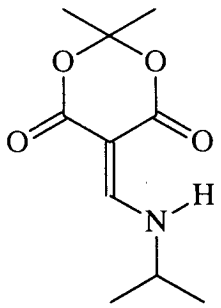


121



122

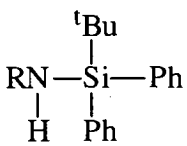
Unfortunately, the expected product **122** was not formed and only compound **123**, the deprotected product was isolated.



123

This result indicated cleavage of the N-Si bond under these reaction conditions, probably by the methanol by-product of the desired initial reaction of **89** with the protected amine. Reaction of the protected amine **121** with methanol also resulted in deprotection, supporting this hypothesis.

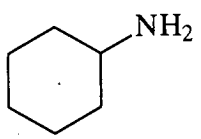
A report in the literature from Overman *et al* [113] discussed the use of the *t*-butyldiphenylsilyl (TBDPS) group **124** as a protecting group for primary amines.



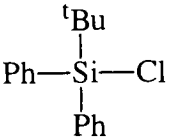
124

The paper reported selective protection of primary amines in the presence of secondary amines, the ease of deprotection with 80% acetic acid at room temperature, but most significantly, the stability of TBDPS protected amines to hydrolytic and strongly basic reagents - a vital consideration in the Meldrum's acid route, given results of previous work discussed earlier.

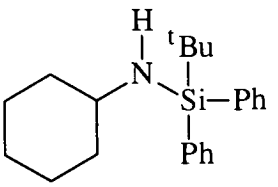
For our work the most appropriate protected amine reported in the paper was cyclohexylamine, so this was chosen for synthesis. Using the literature method, cyclohexylamine **125** was reacted with *t*-butyldiphenylsilylchloride (TBDPS-Cl) **126**, in the presence of 1.5 equivalents of triethylamine, using acetonitrile as solvent. This was expected to produce the protected amine **127**.



125



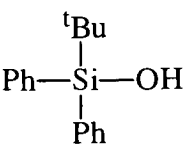
126



127

However, the reaction product gave a ^{1}H NMR spectrum which contained two *t*-butyl peaks instead of the expected one. Extending the reaction time from 3 h to 24 h on the assumption one peak was unreacted starting material made no significant difference to the product composition.

As these compounds were reported to be stable to chromatography the product was subjected to dry flash column chromatography in order to separate the components. However, the only product obtained from the column was *t*-butyldiphenylsilanol **128**, the hydrolysis product.

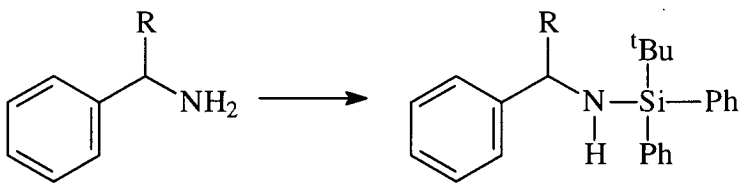


128

This indicated there was a problem with competitive hydrolysis, so precautions were taken to dry the solvent and amine and to work under an atmosphere of nitrogen. The more detailed experimental procedure of Wills *et al* [114] was also followed. These alterations reduced the proportion of compound **128** produced, but failed to eliminate it completely. Kugelrohr distillation also failed to purify the protected amine any further.

In the hope of an improved reaction, two different amines were selected, benzylamine **129a** and α-methylbenzylamine **129b** and reacted with TBDPS-Cl, again using the method of Wills *et al*, in combination with dry conditions and reagents.

Both compounds produced the desired *N*-silyl protected products **130a** and **130b** (identified by ^{1}H NMR spectroscopy), and the reactions proceeded more cleanly than with cyclohexylamine.

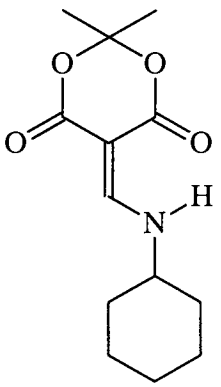


129 **130**

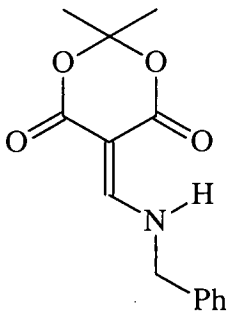
(**a**) R = H (**a**) R = H
(**b**) R = CH_3 (**b**) R = CH_3

Mass spectra of all three products **127**, **130a** and **130b** showed a characteristically intense peak at M^+-C_4H_9, i.e., loss of the *t*-butyl group from the compound, confirming successful protection of the amine by the TBDPS group.

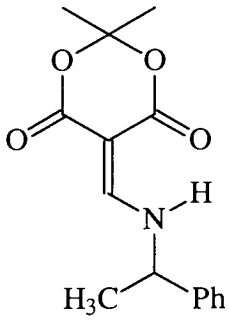
As stated previously, the reaction of an amine with 5-methoxymethylidene Meldrum's acid is extremely facile and the TBDPS-protected derivatives were expected to react smoothly under our standard conditions. However, reaction of the three *N*-silyl protected compounds **127**, **130a** and **130b** under these conditions gave the products **100**,[97] **131** and **132**[97] respectively, comparable to compound **123** obtained previously by Hunter and McNab when working with the TMS protecting group.



100



131



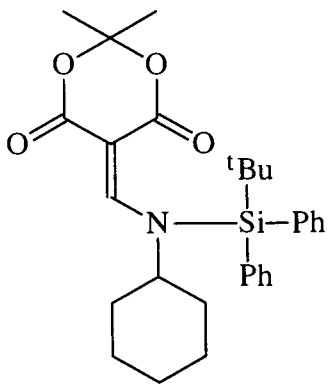
132

The ^{1}H NMR spectra for the three compounds all contained a characteristic doublet at δ_H ~ 8.2 p.p.m. due to the methylidene proton with a coupling constant in the range 14-15 Hz. The coupling arose from the trans interaction between this proton and the NH. Compound **100** was isolated in a moderate yield of 55% and compounds **131** and **132** in higher yields of 80% and 81% respectively.

In an attempt to overcome the problem of in-situ deprotection of the nitrogen atom, alternative conditions[90] were tried. It was hoped that using a much less polar solvent would significantly reduce the amount of hydrolysis occurring; consequently the reaction between protected amine **130b** and 5-methoxymethylidene Meldrum's acid was carried out in refluxing cyclohexane. Unfortunately, after reactions of 2 h or of 24 h only unreacted starting material was recovered.

In complete contrast to the literature report,[113] the TBDPS group appeared to be unstable to hydrolytic conditions in the experimental work carried out. Problems also occurred repeating the literature syntheses of the protected amines, especially in the case of cyclohexylamine, again due to hydrolysis to produce the unwanted silanol compound **128**.

Considering the structure of the desired products, for example, compound **133**, illustrates the hindered nature of the molecule.



133

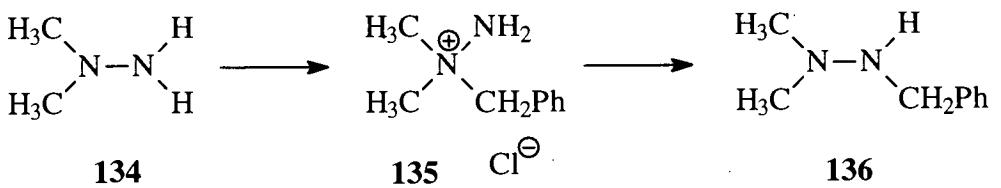
The two substituents present on the nitrogen atom, namely the cyclohexyl and the *t*-butyldiphenylsilyl groups, are extremely bulky and, in conjunction with the Meldrum's acid ring, could be expected to cause much steric hindrance within the molecule; this would make the molecule much more susceptible to loss of one of these groups, namely the silyl protecting group.

Due to the very disappointing results obtained, this line of work was not continued further. Future developments in silicon-based protecting groups could merit a return to this particular protecting group strategy.

3. The Hydrazine Protecting Group

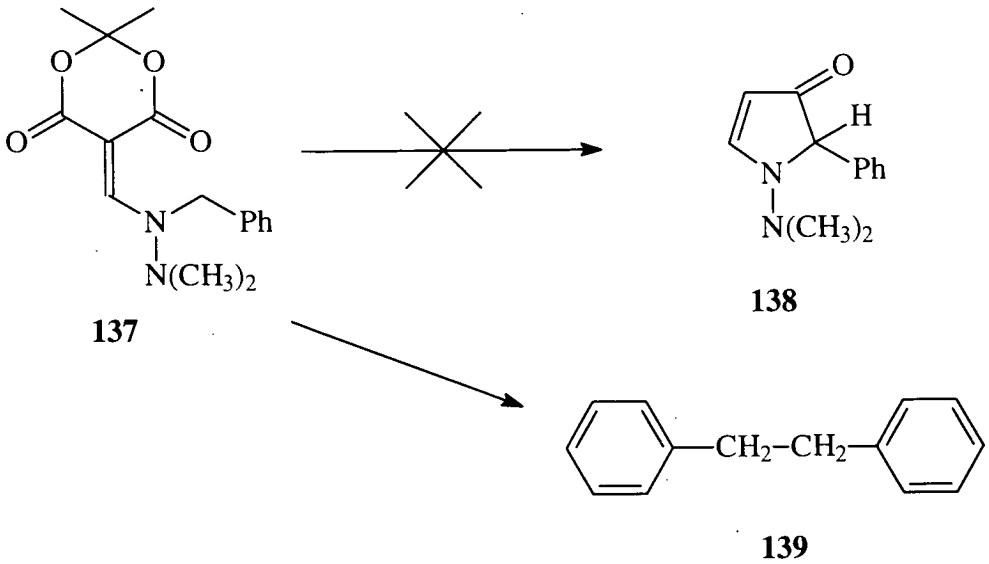
As an alternative to using amines to produce the desired nitrogen-containing heterocycle, hydrazines were considered. These molecules have a built-in NR^1R^2 protecting group on the nitrogen, which could be cleaved reductively at a later stage in the synthesis when the pyrrolone manipulation was complete.

An appropriately substituted hydrazine **136** was chosen, and synthesised.[115] Commercially available *N,N*-dimethylhydrazine **134** was reacted with benzyl chloride to produce the quaternary hydrochloride salt **135** in 71% yield. The salt was then mixed with crushed potassium hydroxide pellets and distilled by Kugelrohr to give the desired hydrazine **136**.



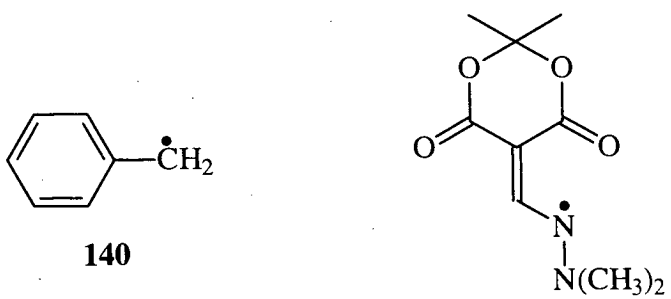
Reaction of hydrazine **136** with 5-methoxymethylidene Meldrum's acid proceeded smoothly, using the same conditions as applied with amines, to produce the aminomethylidene derivative **137**.

However, pyrolysis of the compound failed to give the pyrrolone **138** and much insoluble polymer was generated. Chromatography of the soluble portion of the product yielded only one identifiable product, bibenzyl **139**.



137 138 139

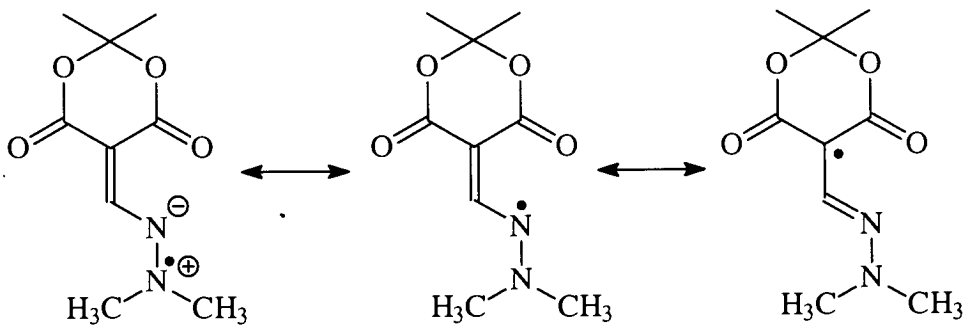
This product arose from the radical cleavage of the aminomethylidene derivative to give the radicals **140** and **141**. Although **140** is a primary radical, it has extra stabilisation provided by the adjacent phenyl group. Dimerisation of this radical produced the isolated product, bibenzyl **139**.



140 141

The second radical **141** can be classed as captodative, a concept developed by Viehe *et al.*[116] The captodative effect is the stabilisation provided to a radical centre by the combined action of an electron-withdrawing substituent and an electron-donating substituent on that centre. In radical **141**, the $N(CH_3)_2$ group acts as the electron-donor, and the methylidene Meldrum's acid portion as the

electron-withdrawer. The radical centre can be delocalised into either of these groups, as illustrated in **Scheme 16**.

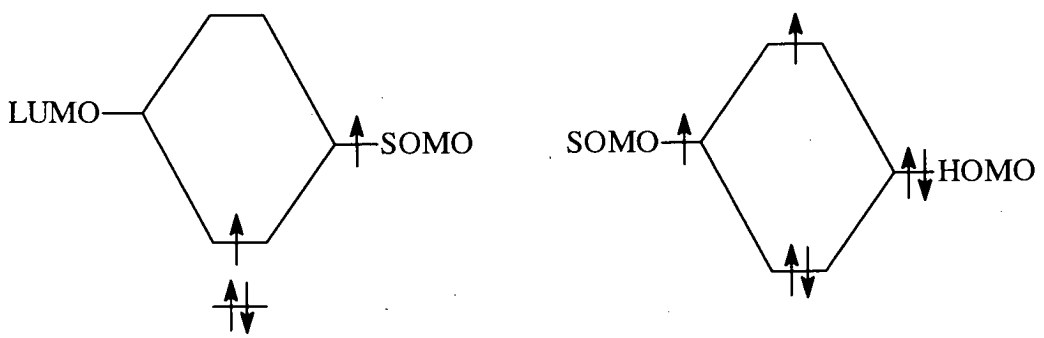


142 **141** **143**

Scheme 16

In the scheme, **142** and **143** represent the conjugative stabilising effect of the α-donor and α-acceptor groups respectively (c.f. Ref 116).

Scheme 17 illustrates the orbital interactions that are responsible for the stabilisation of a radical centre by an acceptor, A and a donor, D.



(**a**) Acceptor (**b**) Donor

Scheme 17

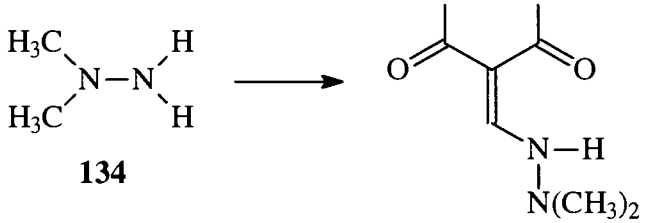
In (**a**) there is an interaction between the radical's singly occupied molecular orbital (SOMO) and the acceptor's lowest unoccupied molecular orbital (LUMO). This

results in a lowering in energy of the singly occupied molecular orbital of the substituted radical.

In (**b**), the donor stabilises the system *via* a three electron interaction, and the resulting singly occupied orbital is higher in energy than the radical SOMO. Consequently a donor substituted radical is more nucleophilic compared to the unsubstituted version. There is an overall lowering in energy of the system due to the lowering in energy of the HOMO of the donor, which is doubly occupied.

The combined stabilising effect of (**a**) and (**b**), which is present in radical **141**, could explain why radical cleavage occurred in preference to the desired cyclisation to the pyrrolone.

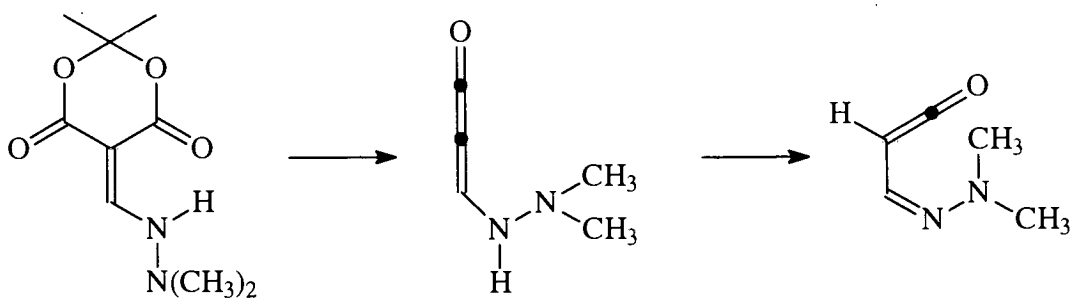
The commercially available hydrazine *N,N*-dimethylhydrazine **134** was also successfully reacted with 5-methoxymethylidene Meldrum's acid to give the aminomethylidene derivative **144** in good yield.



134 **144**

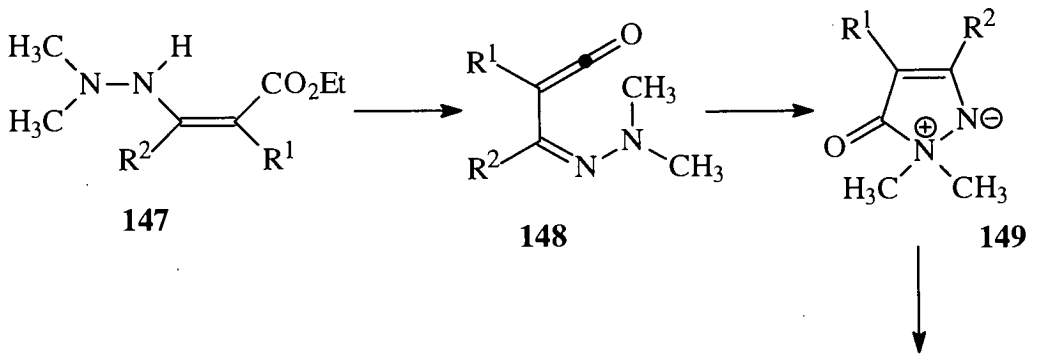
As compound **144** contains an NH, it would not be expected to cyclise to a pyrrolone. However, the intermediates that would be generated by pyrolysis are very similar to those reported in the literature by Chuche *et al* [117] that went on to form pyrazolinones

150. The pyrolysis intermediates of compound **144** are shown in **Scheme 18** and Chuche's work is illustrated in **Scheme 19**.



144 **145** **146**

Scheme 18



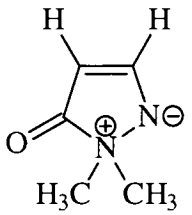
147 **148** **149**

(**a**) $R^1 = CN$, $R^2 = H$
(**b**) $R^1 = CO_2Et$, $R^2 = H$
(**c**) $R^1 = CO_2Me$, $R^2 = H$

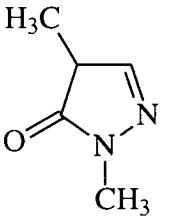
Scheme 19

150

From the schemes the similarities between intermediates **146** and **148** are obvious, and it could therefore be expected that pyrolysis of compound **144** would produce the pyrazolinium ylide **151** and subsequent pyrazolinone **152**, by following Chuche's route.



151



152

However, the pyrolysis was very poor, with insoluble polymeric material obtained as the main product; chromatography of the small soluble portion yielded no identifiable compounds. Altering the pyrolysis temperature had no visible effect on the reaction.

Re-examination of Chuche's reaction scheme provides a possible answer to the failure of the pyrolysis. Cyclisation of the ketene **148** produced the pyrazolinium ylide **149**, and in the examples shown, substituent R^1 was always an electron-withdrawing group. This provided extra stability for the pyrazolinium ylide intermediate by allowing delocalisation of the negative charge on the nitrogen atom through the molecule into the substituent. These intermediates were so stable they could be isolated from the reaction and it was possible to obtain a crystal structure.

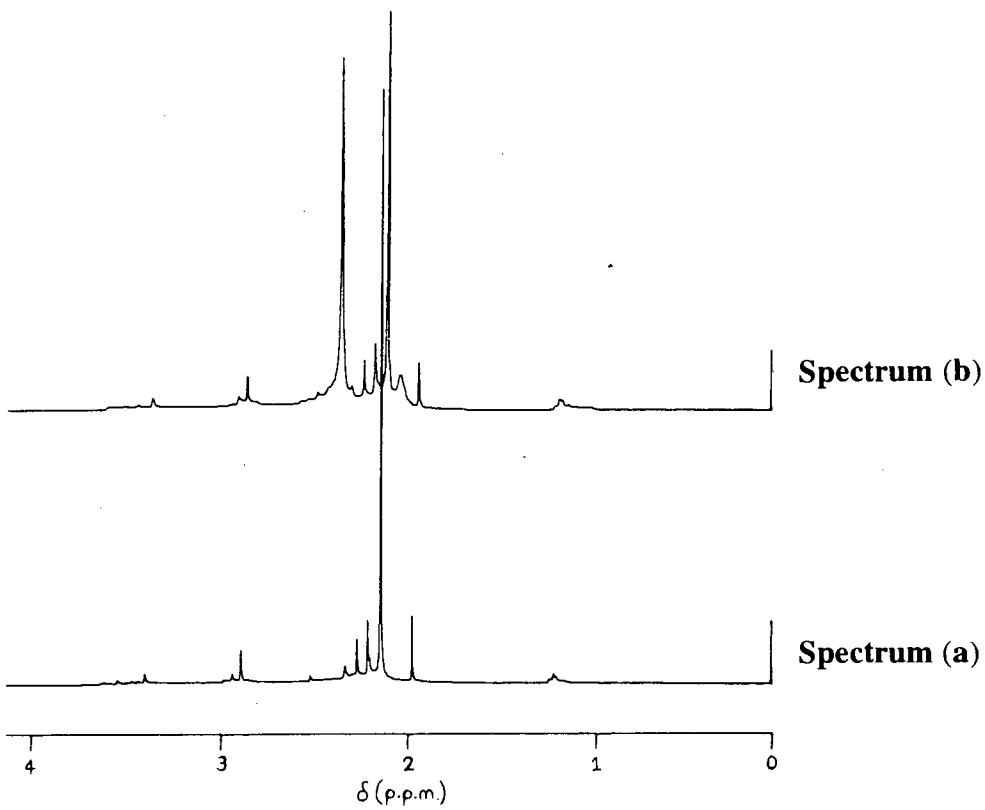
Comparing Chuche's intermediate **149** with the predicted ylide intermediate **151** from the pyrolysis it can be seen that, in **151**, R^1 is a hydrogen atom; this would provide the ylide structure with no extra stabilisation, consequently making its formation much less favourable.

Another possibility to consider was the cleavage of the N-N bond during the pyrolysis. This would generate the highly volatile compound dimethylamine, which has a boiling point of only 7 °C. Standard work-up of FVP products would not trap

this product so an alternative approach was required if this compound was to be isolated.

Before the aminomethylidene derivative **144** was pyrolysed, approximately 1 cm^3 of deuteriated chloroform was distilled into the evacuated U-shaped trap whilst the trap was immersed in liquid nitrogen. The pyrolysis was then performed, and upon completion a further 1 cm^3 of deuteriated chloroform was distilled into the trap, still under vacuum, in liquid nitrogen. The idea behind this strategy was as the trap was slowly allowed to warm to room temperature, any products formed would dissolve in the "sandwich" of deuteriated solvent, and effectively be trapped.

The pyrolysate was examined by ^1H NMR spectroscopy, and then the sample was spiked with a very small amount of commercially available dimethylamine and the spectrum rerun. Spectra obtained are shown in **Scheme 20**.



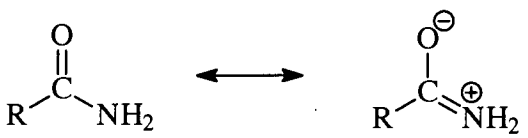
Scheme 20

Spectrum (**a**) shows the ^{1}H NMR of the crude pyrolysate. **Spectrum** (**b**) shows the ^{1}H NMR of the crude pyrolysate spiked with dimethylamine. Comparison of the two spectra show the dimethyl peak of dimethylamine at 2.35 p.p.m. in **spectrum** (**b**) did not coincide with any of the peaks in the pyrolysate ^{1}H NMR **spectrum** (**a**), indicating dimethylamine was not a product of the pyrolysis.

The failure to produce any identifiable products from pyrolysis of the aminomethylidene Meldrum's acid derivatives prepared from hydrazines that would further the route to *N*-protected pyrrolones resulted in this line of investigation being halted and a different protecting group strategy being sought.

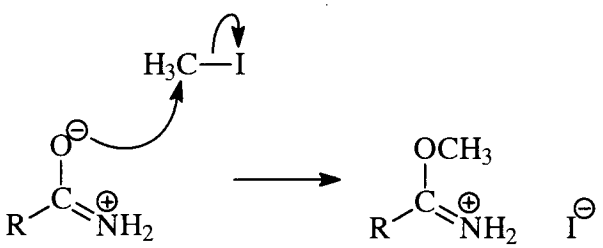
B. REACTIONS OF 5-METHOXYMETHYLIDENE MELDRUM'S ACID WITH PRIMARY AMIDES - SYNTHESIS OF OXAZINONES

Amides are not generally known for their *N*-nucleophilic character. Due to their structure, the lone pair on the nitrogen atom can be delocalised through the molecule, as illustrated in **Scheme 21**.



Scheme 21

This results in the nucleophilicity of the nitrogen atom being much reduced when compared to, for example, amines, and also results in the compounds being able to act as *O*-nucleophiles, such as in the methylation reaction illustrated in **Scheme 22**.



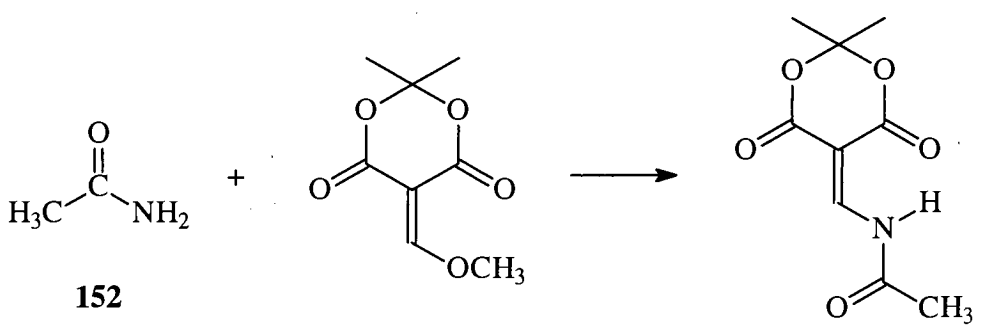
Scheme 22

Further substitution of the nitrogen atom to give secondary and tertiary amides would be expected to further inhibit the *N*-nucleophilic character due to increased steric hindrance at this site.

1. Reactions of Primary Amides[118]

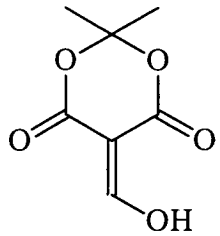
For simplicity, the reactions of primary amides with 5-methoxymethylidene Meldrum's acid were studied initially; this would remove any problems of steric hindrance at the nitrogen atom, leaving only the consideration of general reactivity and *O*-nucleophilic 'vs' *N*-nucleophilic action.

Reaction of acetamide **152** with 5-methoxymethylidene Meldrum's acid **89** in acetonitrile at room temperature, very suprisingly, gave the amidomethylidene Meldrum's acid derivative **153a**.[118] This indicated that the amide was acting as an *N*-nucleophile rather than an *O*-nucleophile, the desired result for this area of work.



152 **89** **153a**

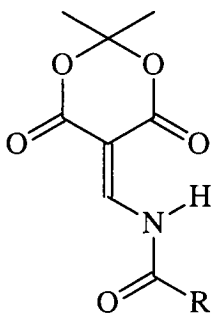
However, these conditions gave a yield of only 36% of compound **153a**. Increasing the reaction time to try to improve the yield was moderately successful, but examination of the crude reaction product by ^{1}H NMR spectroscopy showed the presence of 5-hydroxymethylidene Meldrum's acid **154**, the hydrolysis product from 5-methoxymethylidene Meldrum's acid, indicating this reagent was not surviving the extended reaction times.



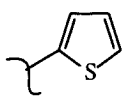
154

As an alternative to improve the yield, the reaction was heated under reflux; this was monitored by obtaining ^{1}H NMR spectra of aliquots of the mixture at various time intervals in order to optimise the length of the reaction. A reaction time of 24 h gave a significantly improved yield of 62% of compound **153a** after recrystallisation.

Following the success of this reaction, a variety of amides were reacted with 5-methoxymethylidene Meldrum's acid, and this produced a range of amidomethylidene Meldrum's acid derivatives **153b-f**.[118]



153

(**b**) R = CH_2CH_3
(**c**) R = $CH(CH_3)_2$
(**d**) R = $C(CH_3)_3$
(**e**) R = C_6H_5
(**f**) R = 

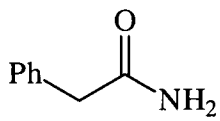
However across the range of amides used, reaction times and yields were very variable, as illustrated in **Table 3**.

In the case of the 2-thienyl derivative **153f**, a reaction time of 96 h was required to obtain the moderate yield of 51%. The reaction involving *iso*-butyramide (to produce **153c**) gave an optimum yield of only 24%.

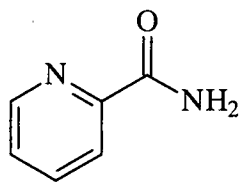
Table 3

Compound	Reaction Time (h)	Yield (%)
153a	24	62
153b	24	58
153c	48	24
153d	72	48
153e	48	48
153f	96	51

A major factor in these reactions was the solubility of the starting amide, which in many instances was quite poor, even in refluxing acetonitrile; this significantly affected the yields obtained *via* this route. Two further amides, phenylacetamide **155** and nicotinamide **156** failed to give any of the desired aminomethylidene product, and starting material was recovered. Extended reaction times resulted only in decomposition.

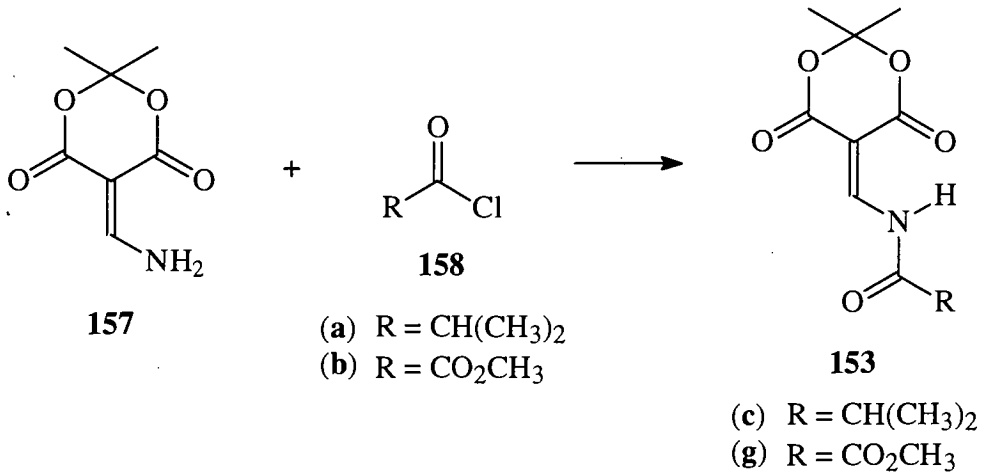


155



156

Due to the problems encountered, an alternative route was sought into these amidomethylidene systems, utilising the reaction between an amine and an acid chloride. Aminomethylidene Meldrum's acid[94] **157** was heated under reflux with *iso*-butyryl chloride **158a** in the presence of triethylamine again using acetonitrile as the solvent. This produced the desired amidomethylidene compound **153c** in a much improved yield of 70%. The reaction time was also significantly reduced from 24 h to only 2 h.

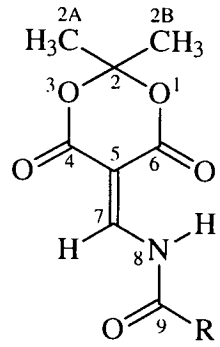


This methodology also allowed an ester substituted amidomethylidene derivative to be prepared, using methyl oxalyl chloride **158b**[118] as a starting material; an 8 h reaction gave a yield of 56% of compound **153g**.

Table 4 illustrates the ^{13}C and selected ^{1}H chemical shift values for the amidomethylidene Meldrum's acid derivatives **153a-g** prepared. All spectra were recorded in $CDCl_3$ unless otherwise stated.

The ^{1}H chemical shifts quoted show consistency across the range of amido substituents. The coupling constant between H(8) and H(7) (approximately 12.6 Hz) is typical for the trans arrangement of these two protons, relative to the C(7)-N(8) bond.

The chemical shift values for the Meldrum's acid ring carbon atoms and C(7) are also very consistent, with the substituent, R, having little effect, except in the case of the ester **153g**. The presence of this strongly electron-withdrawing group had a deshielding effect on C(5) and a shielding effect on C(7), at least in part due to the lone pair of the nitrogen atom being predominantly delocalised into the amide substituent.



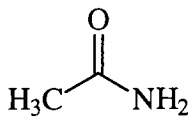
153

Table 4

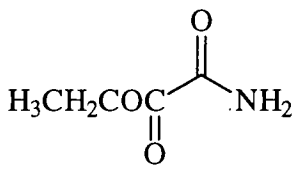
Compound **153**	Chemical Shift (p.p.m.)										^3J (Hz)
	C(2)	C(2A) & (2B)	C(4)/C(6)	C(5)	C(4)/C(6)	C(7)	C(9)	CH_3 (2A) & (2B)	H(7)	H(8)	H(7)-H(8)
a	105.35	26.98	161.62	93.13	163.81	149.76	168.06	1.64	8.70	10.94	12.5
b	105.24	26.91	161.62	92.90	163.86	149.76	171.68	1.62	8.72	10.94	12.8
c	105.45	27.09	161.68	93.29	164.24	150.27	174.70	1.68	8.80	11.12	12.7
d	105.45	27.09	161.62	93.40	164.48	150.71	176.27	1.67	8.79	11.46	12.6
e	105.54	27.06	161.48	94.03	163.62	150.62	164.56	1.72	9.02	12.08	12.4
f*	105.73	26.87	161.74	93.97	163.48	149.59	158.54	1.71	8.65	11.71	12.5
g	105.98	27.30	161.02	97.32	163.21	147.78	158.03	1.71	8.70	12.08	12.7

* [$^2H_6$]DMSO

The lowering of the chemical shift of the C(9) carbonyl carbon atom is consistent with the ^{13}C NMR spectra of simple amides. Acetamide **152** has a carbonyl carbon atom chemical shift of 173.06 p.p.m. whereas ethyl oxamate **159** has carbonyl carbon atom chemical shifts of 160.98 p.p.m. and 158.98 p.p.m., both of which are significantly lower than acetamide.



152



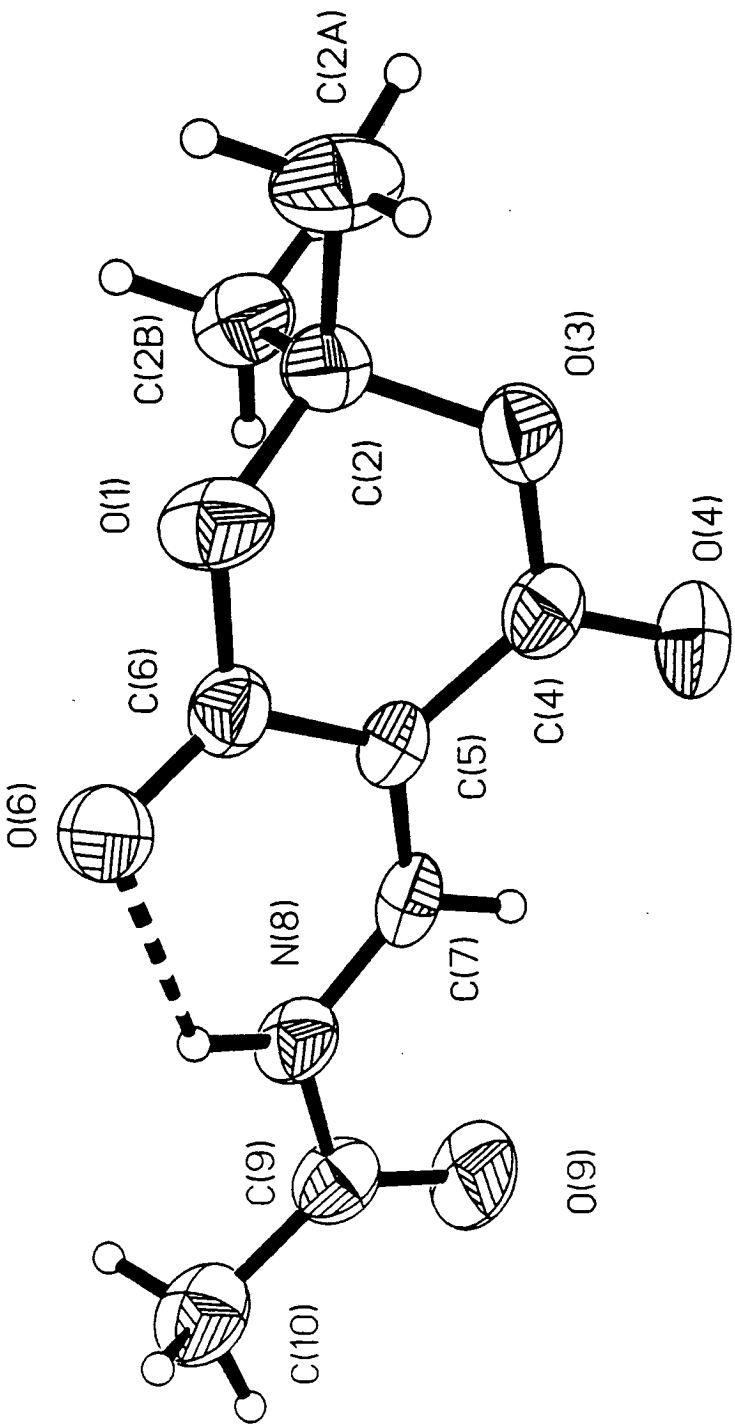
159

When subjected to electron impact mass spectrometry, all of the derivatives showed significant molecular ions, with the initial breakdown peak of loss of M^+ - 57 or 58 corresponding to loss of (acetone - H) or acetone respectively. Loss of carbon dioxide, or of alkyl substituents competed for the later fragmentations. This trend is typical of Meldrum's acid derivatives.

The crystal structures of two of the derivatives **153a** and **153g** were determined. These are shown in **Schemes 23** and **24** respectively, along with their relevant bond lengths, bond angles and torsion angles in **Tables 5**, **6** and **7** and **Tables 8**, **9** and **10**.

Both compounds exhibit the same overall geometry, i.e., the amide carbonyl unit is trans to the NH with respect to the N(8)-C(9) bond.

The two derivatives both have the potential to form six membered hydrogen bonded rings between the NH and carbonyl oxygen atom in the Meldrum's ring, and the O···H(8) distances of 2.225(6) Å in **153a** and 2.16(3) Å in **153g** reflect this. The angle C(5)-C(7)-N(8) in compound **153g** is smaller than in **153a**, resulting in a tighter six-membered ring and shorter O(4)···H(8) hydrogen bonded distance.



Scheme 23

Table 5 - Bond Lengths (Å)

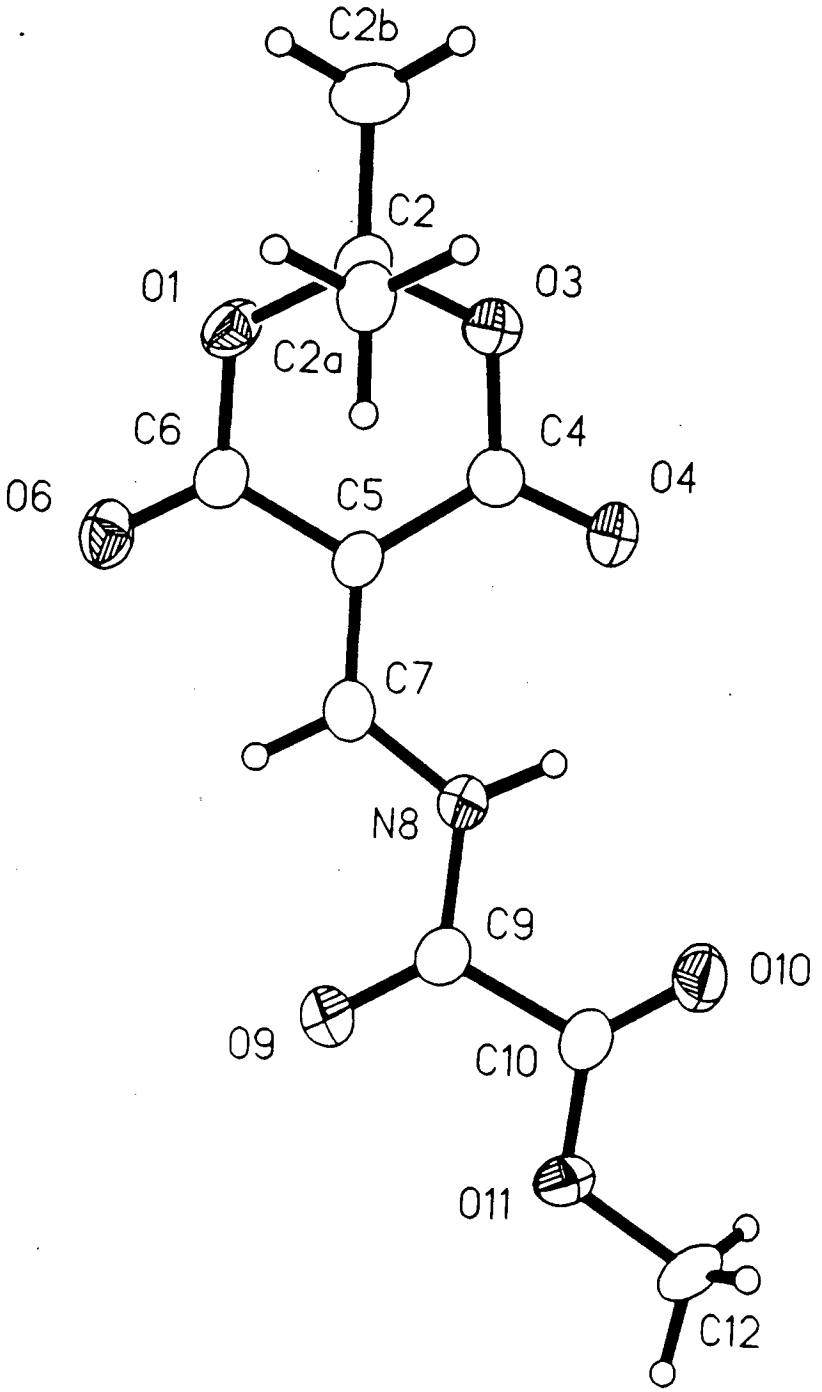
O(1)-C(6)	1.365(5)
O(1)-C(2)	1.443(5)
C(2)-O(3)	1.432(6)
C(2)-C(2B)	1.511(7)
C(2)-C(2A)	1.512(7)
O(3)-C(4)	1.366(6)
C(4)-O(4)	1.199(6)
C(4)-C(5)	1.476(7)
C(5)-C(7)	1.360(7)
C(5)-C(6)	1.434(7)
C(6)-O(6)	1.217(5)
C(7)-N(8)	1.351(6)
N(8)-C(9)	1.409(6)
O(9)-C(9)	1.203(6)
C(9)-C(10)	1.501(7)
H(8)-O(6)	2.255(6)

Table 6 - Bond Angles (degrees)

C(6)-O(1)-C(2)	116.9(4)
O(1)-C(2)-O(3)	110.4(4)
O(1)-C(2)-C(2B)	110.5(4)
O(3)-C(2)-C(2B)	110.9(4)
O(1)-C(2)-C(2A)	105.5(4)
O(3)-C(2)-C(2A)	106.6(4)
C(2B)-C(2)-C(2A)	112.8(4)
C(4)-O(3)-C(2)	118.8(4)
O(4)-C(4)-O(3)	120.0(4)
O(4)-C(4)-C(5)	125.9(4)
O(3)-C(4)-C(5)	114.0(4)
C(7)-C(5)-C(4)	115.9(4)
C(7)-C(5)-C(6)	123.2(4)
C(4)-C(5)-C(6)	120.7(4)
O(6)-C(6)-O(1)	117.0(4)
O(6)-C(6)-C(5)	125.7(4)
O(1)-C(6)-C(5)	117.3(4)
N(8)-C(7)-C(5)	127.6(5)
C(7)-N(8)-C(9)	119.3(4)
O(9)-C(9)-N(8)	122.1(4)
O(9)-C(9)-C(10)	124.1(4)
N(8)-C(9)-C(10)	113.8(4)

Table 7 - Torsion Angles (degrees)

C(6)-O(1)-C(2)-C(3)	-48.9(5)
C(6)-O(1)-C(2)-C(2B)	74.2(5)
C(6)-O(1)-C(2)-C(2A)	-163.6(4)
O(1)-C(2)-O(3)-C(4)	51.7(5)
C(2B)-C(2)-O(3)-C(4)	-71.2(5)
C(2A)-C(2)-O(3)-C(4)	165.7(4)
C(2)-O(3)-C(4)-O(4)	161.3(4)
C(2)-O(3)-C(4)-C(5)	-22.4(5)
O(4)-C(4)-C(5)-C(7)	-8.8(6)
O(3)-C(4)-C(5)-C(7)	175.2(4)
O(4)-C(4)-C(5)-C(6)	165.5(4)
O(3)-C(4)-C(5)-C(6)	-10.5(6)
C(2)-O(1)-C(6)-O(6)	-164.4(4)
C(2)-O(1)-C(6)-C(5)	18.6(5)
C(7)-C(5)-C(6)-O(6)	9.4(7)
C(4)-C(5)-C(6)-O(6)	-164.5(4)
C(7)-C(5)-C(6)-O(1)	-173.9(4)
C(4)-C(5)-C(6)-O(1)	12.2(6)
C(4)-C(5)-C(7)-N(8)	177.5(4)
C(6)-C(5)-C(7)-N(8)	3.4(7)
C(5)-C(7)-N(8)-C(9)	179.9(4)
C(7)-N(8)-C(9)-O(9)	3.5(7)
C(7)-N(8)-C(9)-C(10)	-177.2(4)



Scheme 24

Table 8 - Bond Lengths (Å)

O(1)-C(6)	1.345(3)
O(1)-C(2)	1.450(3)
C(2)-O(3)	1.458(3)
C(2)-C(2B)	1.507(4)
C(2)-C(2A)	1.505(4)
O(3)-C(4)	1.344(3)
C(4)-O(4)	1.224(3)
C(4)-C(5)	1.457(4)
C(5)-C(7)	1.351(4)
C(5)-C(6)	1.471(4)
C(6)-O(6)	1.210(3)
C(7)-N(8)	1.354(3)
N(8)-C(9)	1.383(3)
O(9)-C(9)	1.200(3)
C(9)-C(10)	1.534(3)
C(10)-O(10)	1.200(3)
C(10)-O(11)	1.315(3)
O(11)-C(12)	1.463(3)
O(4)-H(8)	2.16(3)
O(10)-H(8)	2.35(3)

Table 9 - Bond Angles (degrees)

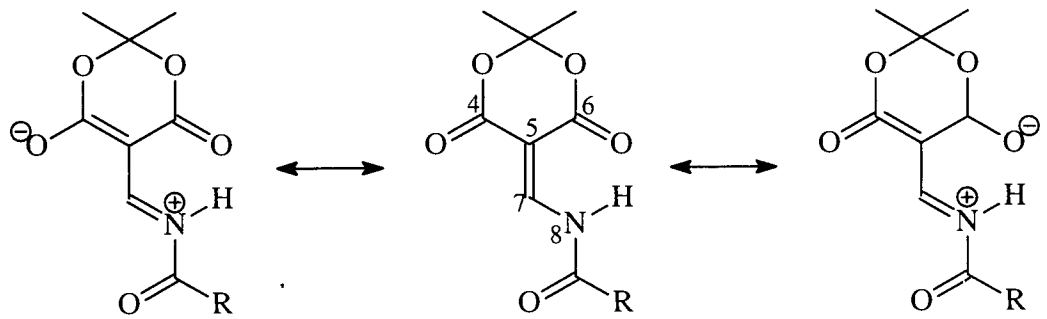
C(6)-O(1)-C(2)	118.9(2)
O(1)-C(2)-O(3)	109.7(2)
O(1)-C(2)-C(2B)	106.1(2)
O(3)-C(2)-C(2B)	105.4(2)
O(1)-C(2)-C(2A)	110.7(2)
O(3)-C(2)-C(2A)	109.9(2)
C(2B)-C(2)-C(2A)	114.8(2)
C(4)-O(3)-C(2)	117.0(2)
O(4)-C(4)-O(3)	118.9(2)
O(4)-C(4)-C(5)	124.3(2)
O(3)-C(4)-C(5)	116.7(2)
C(7)-C(5)-C(4)	122.6(2)
C(7)-C(5)-C(6)	117.6(3)
C(4)-C(5)-C(6)	119.8(2)
O(6)-C(6)-O(1)	119.6(3)
O(6)-C(6)-C(5)	124.5(3)
O(1)-C(6)-C(5)	115.8(3)
N(8)-C(7)-C(5)	125.6(3)
C(7)-N(8)-C(9)	120.5(2)
O(9)-C(9)-N(8)	123.7(2)
O(9)-C(9)-C(10)	124.2(3)
N(8)-C(9)-C(10)	112.1(2)
O(10)-C(10)-O(11)	127.6(3)
O(10)-C(10)-C(9)	122.1(3)
O(11)-C(10)-C(9)	110.4(2)
C(10)-O(11)-C(12)	116.2(2)

Table 10 - Torsion Angles (degrees)

C(6)-O(1)-C(2)-C(3)	48.4(3)
C(6)-O(1)-C(2)-C(2B)	-73.1(3)
C(6)-O(1)-C(2)-C(2A)	161.7(2)
O(1)-C(2)-O(3)-C(4)	-51.6(3)
C(2B)-C(2)-O(3)-C(4)	-165.4(2)
C(2A)-C(2)-O(3)-C(4)	70.4(3)
C(2)-O(3)-C(4)-O(4)	-159.2(2)
C(2)-O(3)-C(4)-C(5)	23.7(3)
O(4)-C(4)-C(5)-C(7)	9.9(4)
O(3)-C(4)-C(5)-C(7)	-173.1(2)
O(4)-C(4)-C(5)-C(6)	-167.2(3)
O(3)-C(4)-C(5)-C(6)	9.8(4)
N(8)-C(9)-C(10)-O(10)	11.9(4)
N(8)-C(9)-C(10)-O(11)	-168.1(2)
C(9)-C(10)-O(11)-C(12)	179.8(2)
C(2)-O(1)-C(6)-O(6)	165.8(2)
C(2)-O(1)-C(6)-C(5)	-17.2(3)
C(7)-C(5)-C(6)-O(6)	-13.7(4)
C(4)-C(5)-C(6)-O(6)	163.6(3)
C(7)-C(5)-C(6)-O(1)	169.5(2)
C(4)-C(5)-C(6)-O(1)	-13.2(3)
C(4)-C(5)-C(7)-N(8)	-0.1(4)
C(6)-C(5)-C(7)-N(8)	177.1(2)
C(5)-C(7)-N(8)-C(9)	173.9(3)
C(7)-N(8)-C(9)-O(9)	4.5(4)
C(7)-N(8)-C(9)-C(10)	-175.9(2)
O(9)-C(9)-C(10)-O(10)	-168.5(3)
O(9)-C(9)-C(10)-O(11)	11.4(4)
O(10)-C(10)-O(11)-C(12)	-0.3(4)

As in all the cases of Meldrum's acid derivatives able to form a six-membered hydrogen bonded ring *via* the NH/carbonyl interaction, the bond lengths within this ring show more of the delocalisation effects than those outside the ring. For example in **153a**, C(5)-C(6) [1.434(7) Å] is shorter than C(4)-C(5) [1.476(7) Å] and C(6)-O(6) [1.217(5) Å] is correspondingly longer than C(4)-O(4) [1.199(6) Å].

Delocalisation of the nitrogen atom lone pair into the Meldrum's acid ring is possible in both compounds, as illustrated in **Scheme 25**.



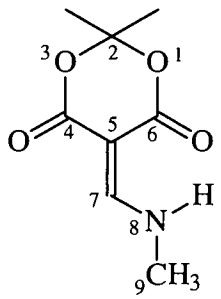
Scheme 25

Contributions by the two resonance structures to the overall structure results in bonds N(8)-C(7), C(4)-C(5) and C(5)-C(6) having some double bond character, and the C(5)-C(7) bond having some single bond character.

The effect is more pronounced in the *N*-acetamido derivative **153a**, for example the longer C(5)-C(7) bond length of 1.360(7) Å compared to that in **153g** of 1.351(4) Å. This can be attributed to further delocalisation of the nitrogen atom lone pair into the amide substituent. The delocalisation in this direction is much more pronounced in compound **153g**, with the ester substituent making the amido group much more strongly electron-withdrawing overall than in compound **153a** in which the amido

group has a methyl substituent. This is reflected in the N(8)-C(9) bond lengths of 1.383(3) Å in the amidoester **153g** compared with 1.409(6) Å in compounds **153a**.

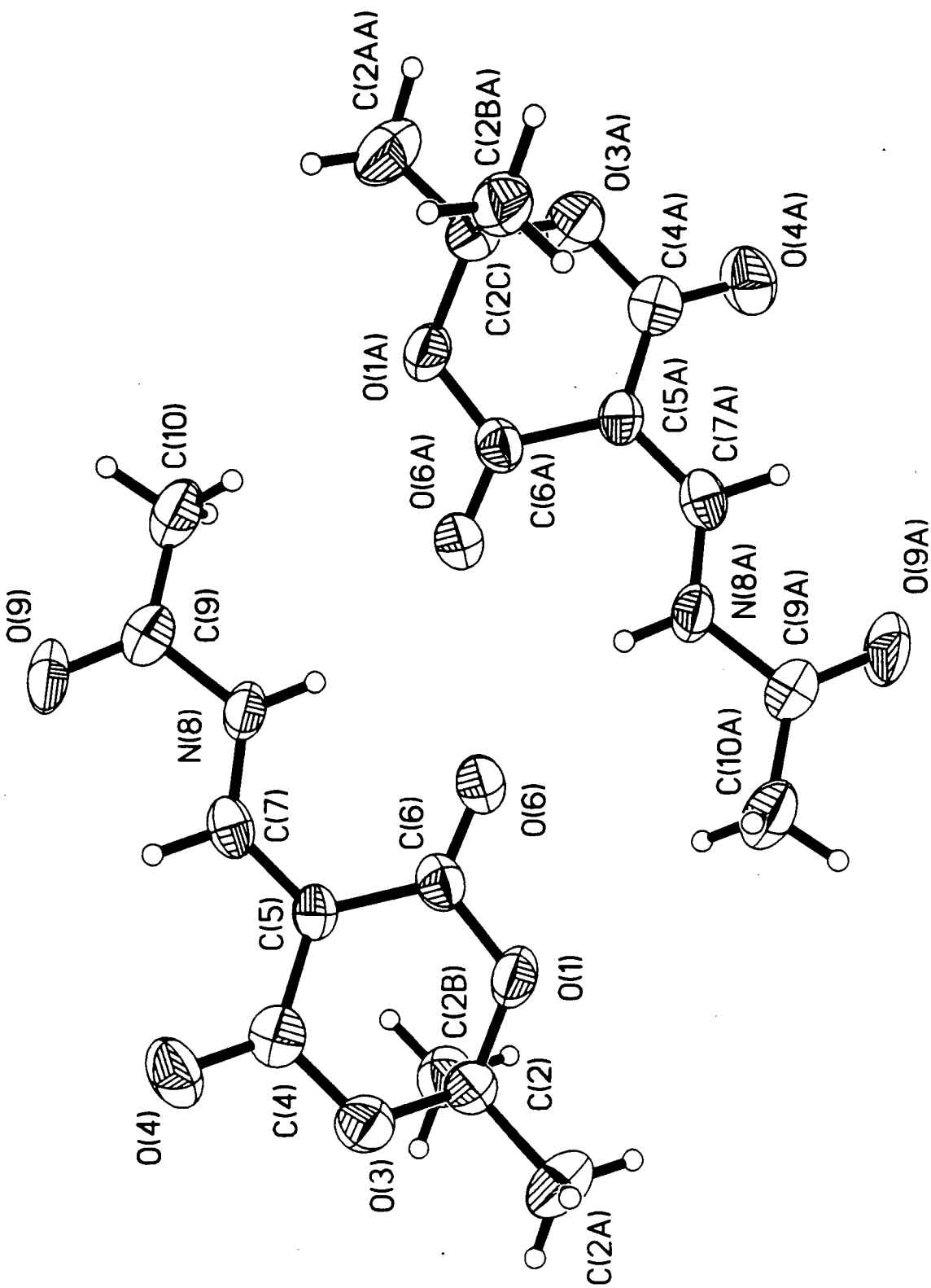
The overall effect of an *N*-amido substituent can be seen when the two X-ray structures are compared with a similar compound lacking the amido electron-withdrawing group, for example compound **160**.[119]



160

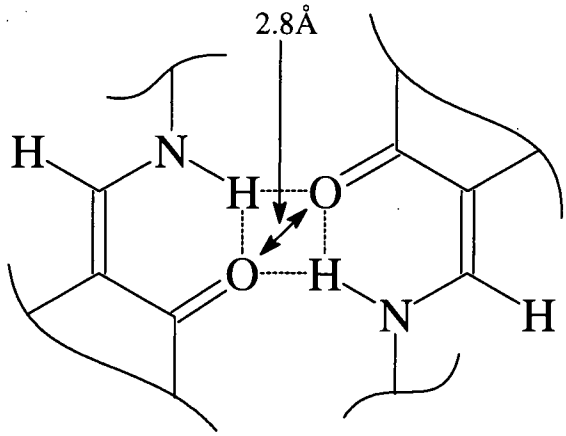
In this *N*-alkyl substituted compound, the lone pair on the nitrogen atom can only delocalise into the Meldrum's acid ring and this is reflected in the N(8)-C(7) bond length [1.281(14) Å] having significant double bond character, and the C(7)-C(5) bond length [1.409(15) Å] having significant single bond character. The effect is much more pronounced in compound **160** than in compounds **153a** or **153g**, due to the latter two structures having other resonance structures available *via* the amide substituents on the nitrogen atom.

Further crystallographic work has shown that the overall structure of the *N*-acetamido derivative is made up of strongly hydrogen bonded pairs of molecules, as illustrated in **Scheme 26**.


C(2AA)
C(2BA)
O(3A)
C(4A)
O(4A)
C(2C)
O(1A)
C(5A)
C(7A)
O(6A)
C(6A)
C(10)
O(9)
C(9)
N(8A)
O(9A)
C(9A)
N(8)
C(10A)
C(7)
C(6)
O(6)
C(5)
C(2B)
O(1)
O(4)
C(4)
C(2)
O(3)
C(2A)

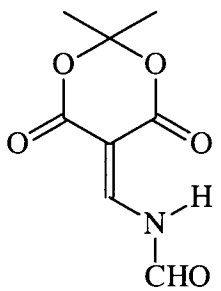
Scheme 26

In the hydrogen bonded region, shown in more detail in **Scheme 27** it can be seen that the strength of the hydrogen bonding has brought the oxygen atoms of carbonyl groups in different molecules significantly close together. The distance between them of only 2.8 Å is highly unusual, most carbonyl groups in separate molecules normally staying a minimum of 3 Å apart.

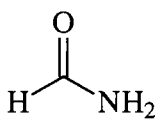


Scheme 27

Following the success of the previous reactions, attempts were made to synthesise the parent aminomethylidene Meldrum's acid derivative **153h**, for which formamide **161** is the required starting material.



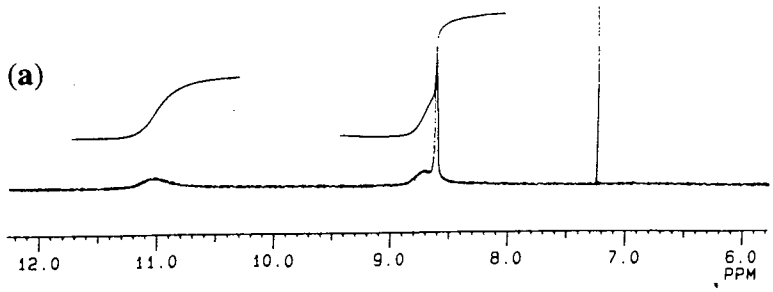
153h



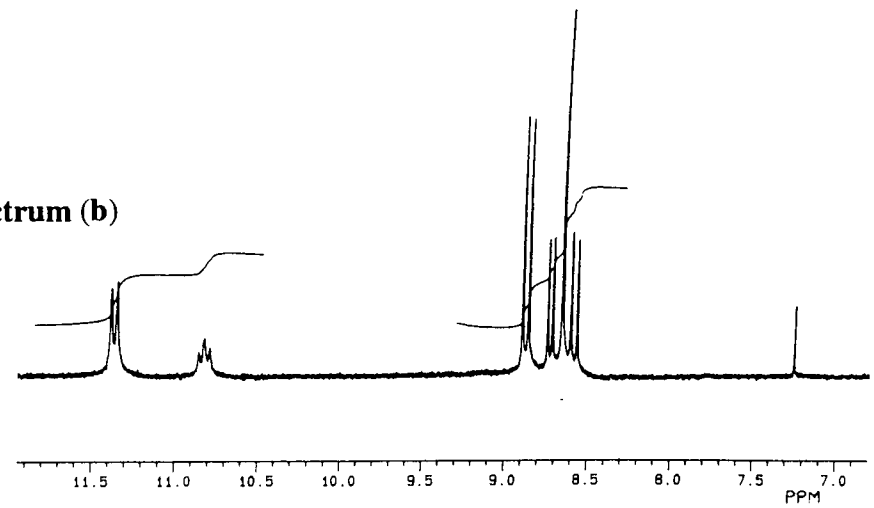
161

When the reaction was monitored by ^1H NMR spectroscopy no starting materials were found to be present after a 96 h reflux. However, the product(s) gave a very broad ^1H NMR spectrum at room temperature in $CDCl_3$, as illustrated in **Scheme 28**, **spectrum (a)**.

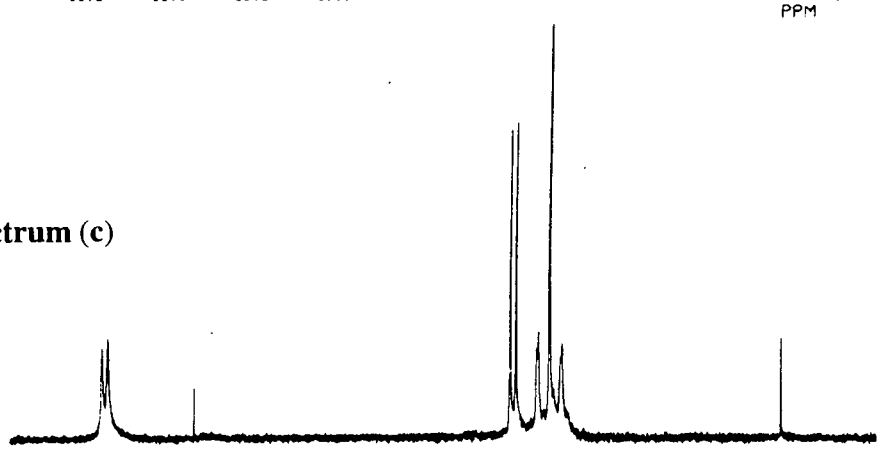
Spectrum (a)



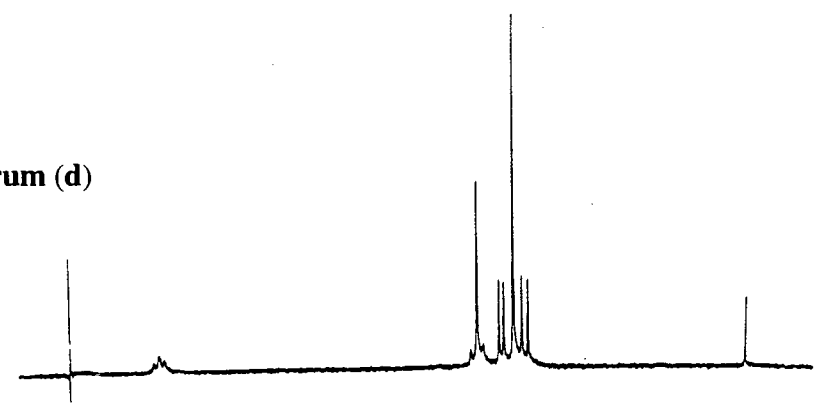
Spectrum (b)



Spectrum (c)



Spectrum (d)

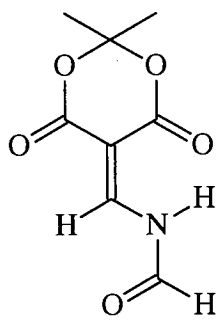


Scheme 28

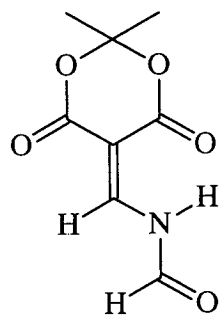
A low temperature 360MHz ^1H NMR spectrum was obtained at -60 °C [**spectrum** (**b**)] and this was subjected to various decoupling experiments, two of which are illustrated in **spectra** (**c**) and (**d**).

Spectrum (**b**) indicated the reaction product was a mixture of two components, in the approximate ratio 2:1. Irradiation of the apparent triplet of the minor component at 10.8 p.p.m. in **spectrum** (**c**) resulted in both of the smaller doublets at 8.6 and 8.7 p.p.m. collapsing to singlets. The large coupling constants (13.4 and 10.3 Hz) in these signals indicated a trans arrangement of the three protons involved. Irradiation of the doublet of the major component at 11.3 p.p.m. in **spectrum** (**d**) collapsed the large doublet at 8.9 p.p.m. to a singlet. The existing singlet at 8.65 p.p.m. (between the two small sets of doublets) was also associated with the major component due to the 1:1:1 integral; this proton was not coupled to the other two, which in turn did couple to each other, with a large coupling constant of 13.0 Hz.

Combining the information collected led to the conclusion that the reaction product was a mixture of the two conformers which are shown in **Scheme 29**.



66%



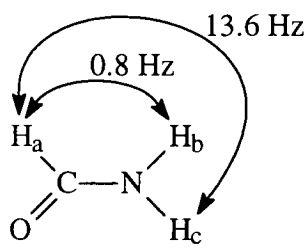
34%

Scheme 29

The minor component on the right in the scheme, gave rise to the triplet, doublet, doublet pattern seen. The NH proton coupled to the methine proton and formyl proton with similar trans coupling constants to give the apparent triplet at 10.8 p.p.m. Coupling of the methine proton to the NH proton, and the formyl proton to the NH proton produced the two doublets at 8.6 and 8.7 p.p.m.

In the major component on the left in the scheme, a large doublet at 8.9 p.p.m. was observed for the methine proton due to coupling to the NH proton. In turn the NH proton coupled to the methine proton giving a doublet at 11.3 p.p.m. No coupling was observed to the formyl proton and correspondingly, the formyl proton appeared as a singlet.

This lack of significant coupling between the NH and formyl proton in a cis arrangement is not unprecedented in the literature.[120] Studies on the ^1H NMR spectrum of formamide itself, as illustrated in **Scheme 30**, have shown that, although the coupling between H_a and H_c has a typical trans coupling constant of 13.6 Hz, the coupling constant for the cis coupling between H_a and H_b is extremely small, at only 0.8 Hz.



Scheme 30

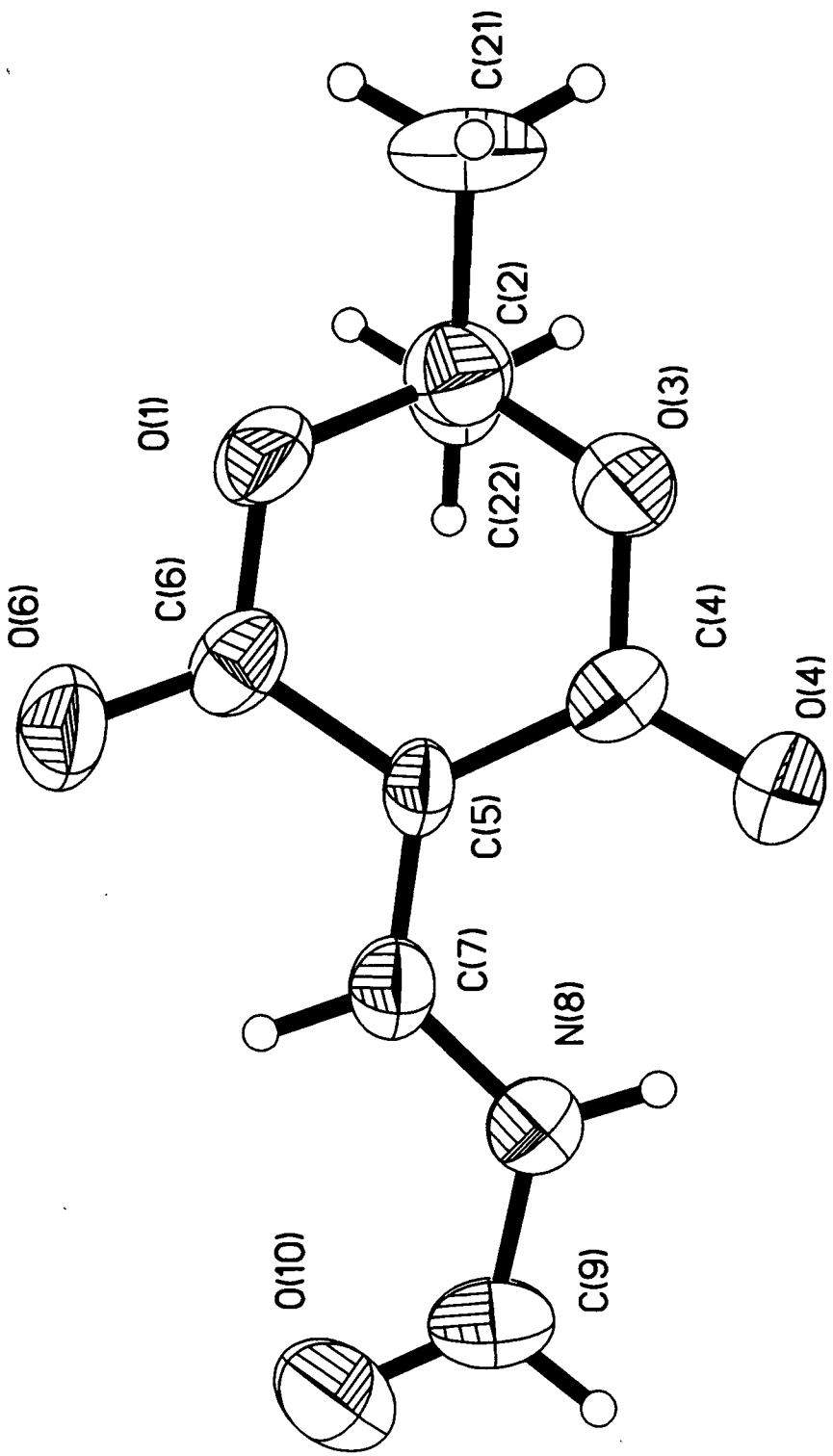
Absolute confirmation of the NMR interpretation was obtained in the form of a crystal structure of the compound. The crystal was found to be disordered and the two conformers found in the solution state were also present in the solid state. The

structures obtained are shown in **Schemes 31** and **32**, along with the relevant bond lengths, bond angles and torsion angles, in **Tables 11**, **12** and **13**.

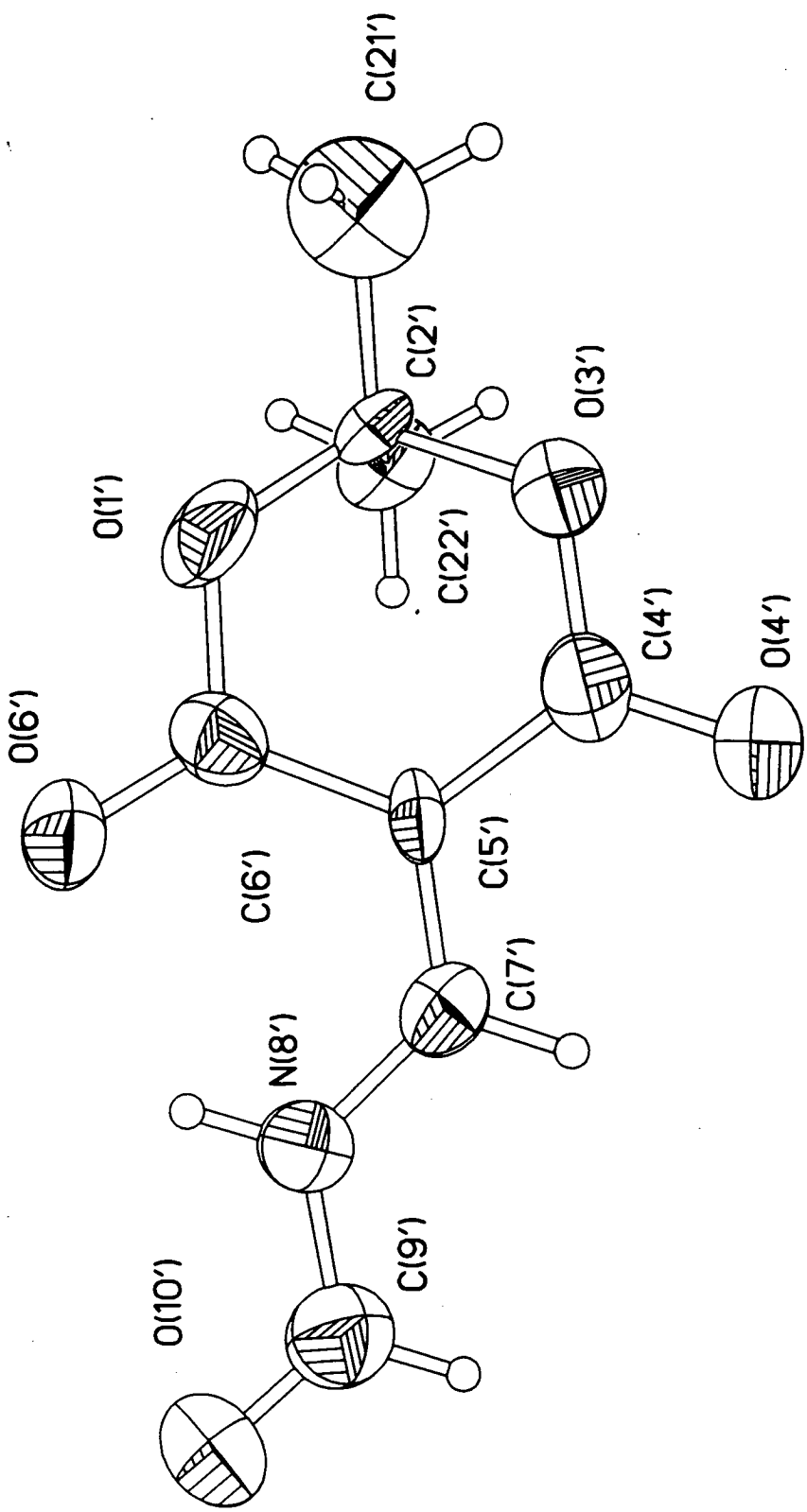
Scheme 31 illustrates the major conformer, and **Scheme 32** the minor. Surprisingly, the two conformers were found to be in almost exactly the same ratio in the solid state as in the solution state, 68:32 compared to 66:34, which is quite unusual, given the exchange at room temperature.

The bond lengths of the two structures are very consistent within experimental error. As with the amidomethylidene crystal structures reported earlier, the molecules can form six-membered intramolecular hydrogen bonded rings, and do so between the carbonyl oxygen atom of the Meldrum's acid ring and the NH.

The structures in **Schemes 31** and **32** show, unsurprisingly, many similarities to the *N*-acetamido derivative in **Scheme 23**. Again, there is a shortening of the C(7)/(7′)-N(8)/(8′) [1.343(4) Å and 1.346(7) Å] and N(8)/(8′)-C(9)/(9′) [1.378(6) Å and 1.370(12) Å] bonds and a lengthening of the C(5)/(5′)-C(7)/(7′) [1.351(6) Å and 1.347(8) Å] bonds in both molecules due to the delocalisation of the lone pair of the nitrogen atom in both directions.



Scheme 31



Scheme 32

Table 11 - Bond Lengths (Å)

O(1)-C(6)	1.348(9)
O(1)-C(2)	1.462(9)
C(2)-O(3)	1.425(9)
C(2)-C(21)	1.504(10)
C(2)-C(22)	1.499(10)
O(3)-C(4)	1.358(7)
C(4)-O(4)	1.228(6)
C(4)-C(5)	1.442(5)
C(5)-C(7)	1.351(6)
C(5)-C(6)	1.458(7)
C(6)-O(6)	1.214(8)
C(7)-N(8)	1.343(4)
N(8)-C(9)	1.378(6)
C(9)-O(10)	1.182(8)
O(1')-C(6')	1.365(13)
O(1')-C(2')	1.427(14)
C(2')-O(3')	1.462(14)
C(2')-C(22')	1.504(16)
C(2')-C(21')	1.491(15)
O(3')-C(4')	1.338(12)
C(4')-O(4')	1.218(12)
C(4')-C(5')	1.432(8)
C(5')-C(7')	1.347(8)
C(5')-C(6')	1.450(10)
C(6')-O(6')	1.214(12)
C(7')-N(8')	1.346(7)
N(8')-C(9')	1.370(12)
C(9')-O(10')	1.184(13)

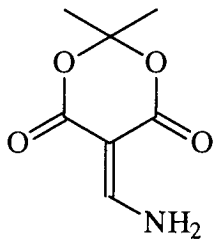
Table 12 - Bond Angles (degrees)

C(6)-O(1)-C(2)	118.8(8)
O(1)-C(2)-O(3)	110.2(7)
O(1)-C(2)-C(21)	104.2(7)
O(3)-C(2)-C(21)	109.3(8)
O(1)-C(2)-C(22)	108.1(9)
O(3)-C(2)-C(22)	111.3(8)
C(21)-C(2)-C(22)	113.5(8)
C(4)-O(3)-C(2)	119.5(7)
O(4)-C(4)-O(3)	117.9(6)
O(4)-C(4)-C(5)	125.2(2)
O(3)-C(4)-C(5)	116.7(5)
C(7)-C(5)-C(4)	122.9(4)
C(7)-C(5)-C(6)	117.5(5)
C(4)-C(5)-C(6)	119.4(5)
O(6)-C(6)-O(1)	117.1(7)
O(6)-C(6)-C(5)	125.2(7)
O(1)-C(6)-C(5)	117.6(7)
N(8)-C(7)-C(5)	126.7(4)
C(7)-N(8)-C(9)	121.9(4)
N(8)-C(9)-O(10)	127.5(7)
C(6')-O(1')-C(2')	119.2(12)
O(1')-C(2')-O(3')	109.9(12)
O(3')-C(2')-C(22')	109.2(12)
O(1')-C(2')-C(22')	111.2(14)
O(3')-C(2')-C(21')	104.4(12)
O(1')-C(2')-C(21')	108.7(12)
C(21')-C(2')-C(22')	113.2(11)
C(4')-O(3')-C(2')	116.4(11)
O(4')-C(4')-O(3')	116.1(9)
O(4')-C(4')-C(5')	125.9(10)
O(3')-C(4')-C(5')	118.0(10)
C(7')-C(5')-C(4')	118.9(7)
C(7')-C(5')-C(6')	120.3(7)
C(4')-C(5')-C(6')	120.6(8)
O(6')-C(6')-O(1')	118.3(10)
O(6')-C(6')-C(5')	127.4(8)
O(1')-C(6')-C(5')	114.3(10)
N(8')-C(7')-C(5')	126.1(6)
C(7')-N(8')-C(9')	124.9(6)
O(10')-C(9')-N(8')	120.5(15)

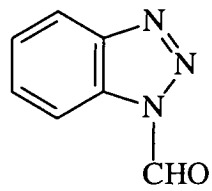
Table 13 - Torsion Angles (degrees)

C(6)-O(1)-C(2)-C(3)	-44.1(16)	C(6')-O(1')-C(2')-O(3')	-50(3)
C(6)-O(1)-C(2)-C(22)	77.7(14)	C(6')-O(1')-C(2')-C(22')	71(2)
O(1)-C(2)-O(3)-C(4)	47.2(14)	C(1')-C(2')-O(3')-O(4')	49(2)
C(6)-O(1)-C(2)-C(21)	-161.3(13)	C(6')-O(1')-C(2')-C(21')	-163(2)
C(22)-C(2)-O(3)-C(4)	-72.7(13)	C(22')-C(2')-O(3')-C(4')	-73.4(19)
C(21)-C(2)-O(3)-C(4)	161.1(10)	C(21')-C(2')-O(3')-C(4')	165.3(18)
C(2)-O(3)-C(4)-O(4)	162.1(9)	C(2')-O(3')-C(4')-O(4')	-162.1(14)
C(2)-O(3)-C(4)-C(5)	-23.0(15)	C(2')-O(3')-C(4')-C(5')	-19(3)
O(4)-C(4)-C(5)-C(7)	-7.6(9)	C(4')-C(4')-C(5')-C(7')	-9.5(18)
O(3)-C(4)-C(5)-C(7)	177.9(8)	C(3')-C(4')-C(5')-C(7')	171.9(15)
O(4)-C(4)-C(5)-C(6)	167.8(8)	C(4')-C(4')-C(5')-C(6')	165.6(14)
O(3)-C(4)-C(5)-C(6)	-6.6(11)	O(3')-C(4')-C(5')-C(6')	-13.2(2)
C(2)-O(1)-C(6)-O(6)	-165.0(11)	O(2')-O(1')-C(6')-O(6')	-162.5(19)
C(2)-O(1)-C(6)-C(5)	17.4(19)	C(2')-O(1')-C(6')-C(5')	20(3)
C(7)-C(5)-C(6)-O(6)	7.4(14)	C(7')-C(5')-C(6')-O(6')	10(2)
C(4)-C(5)-C(6)-O(6)	-168.3(9)	C(4')-C(5')-C(6')-O(6')	-164.5(16)
C(7)-C(5)-C(6)-O(1)	-175.3(11)	C(7')-C(5')-C(6')-O(1')	-171.9(17)
C(4)-C(5)-C(6)-O(1)	9.0(15)	C(4')-C(5')-C(6')-O(1')	13(2)
C(4)-C(5)-C(7)-N(8)	-1.5(6)	C(4')-C(5')-C(7')-N(8')	176.4(8)
C(6)-C(5)-C(7)-N(8)	-177.1(6)	C(6')-C(5')-C(7')-N(8')	1.3(12)
C(5)-C(7)-N(8)-C(9)	178.9(5)	C(5')-C(7')-N(8')-C(9')	178.3(9)
C(7)-N(8)-C(9)-O(10)	2.2(15)	C(7')-N(8')-C(9')-O(10')	173.9(19)

Attempts to synthesise this *N*-formamido derivative by alternative methods were tried, focussing on formylation of aminomethylidene Meldrum's acid **157**.



157

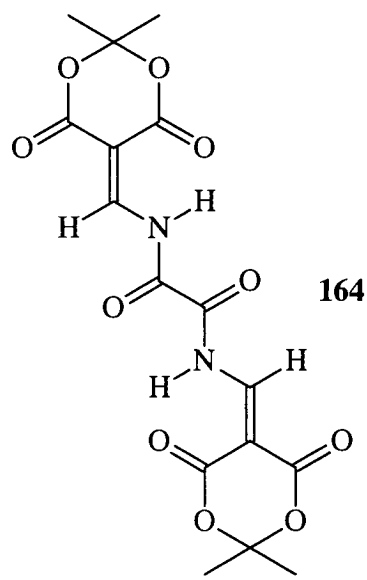


162

N-formyl benzotriazole **162** has been reported as a good formylating agent,[121] but attempts to formylate compound **157** failed, with starting material being quantitatively recovered. Other formylation attempts with acetic formic anhydride[122] and *n*-butyl formate were also unsuccessful.

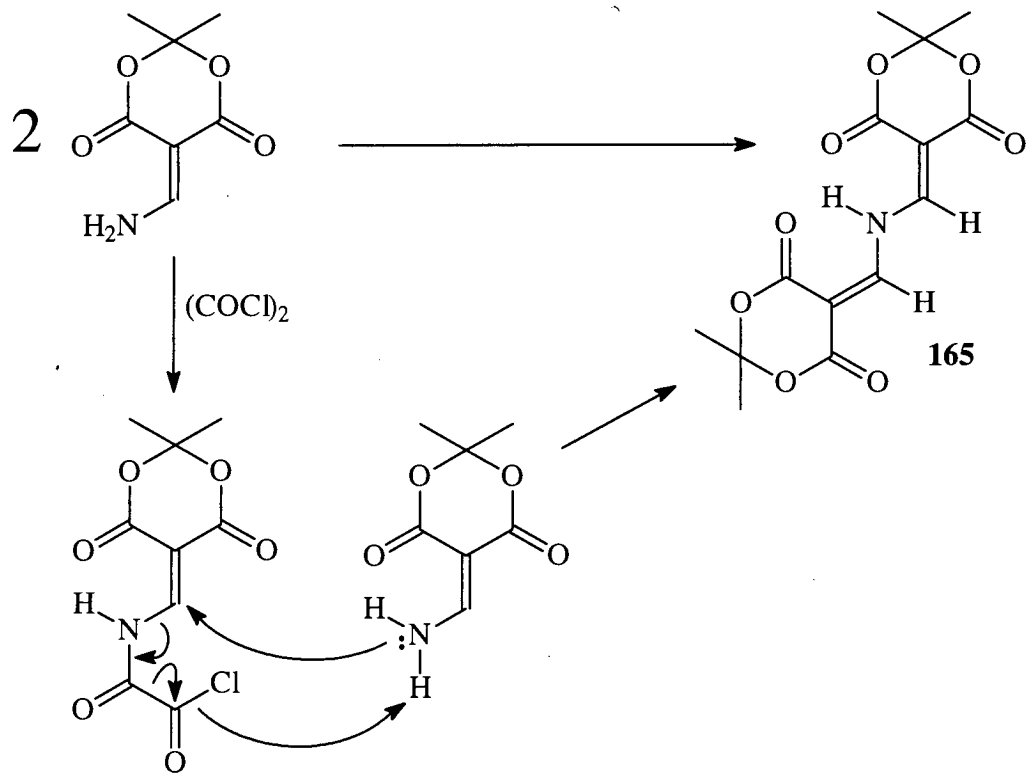
Following the success of the acid chloride route to amidomethylidene derivatives, the reaction of oxalyl chloride **163** with 5-aminomethylidene Meldrum's acid was attempted, with the expectation of producing compound **164** if the correct ratio of starting materials was used.

163



164

However, examination of the reaction product by ^{1}H NMR spectroscopy showed three sets of peaks in the ratio 12:2:1 instead of 12:2:2 as expected. The NH signal (integrating to 1 proton) was a triplet with a coupling constant of 12.7 Hz, indicating a trans coupling to two symmetrically arranged protons. These two protons showed a corresponding doublet at 8.84 p.p.m., a typical δ value for methine protons. This information, analysis of the ^{13}C NMR spectrum, and a molecular ion of *m/z* 325 from electron impact mass spectrometry, indicated the product from the reaction was of structure **165**.

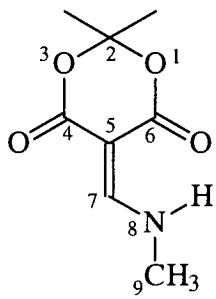


A possible explanation for the formation of the product is as follows: the oxalyl chloride reacted with 5-aminomethylidene Meldrum's acid (in the presence of triethylamine) and the intermediate compound produced then went on to react with another molecule of the aminomethylidene compound (with loss of CO, HNCO and HCl), to produce compound **165**. Repeating the reaction in the absence of oxalyl

chloride, but keeping all other reagents and parameters constant resulted in unreacted starting material being quantitatively recovered, indicating the oxalyl chloride played a significant role in the reaction, although not incorporated in the final product.

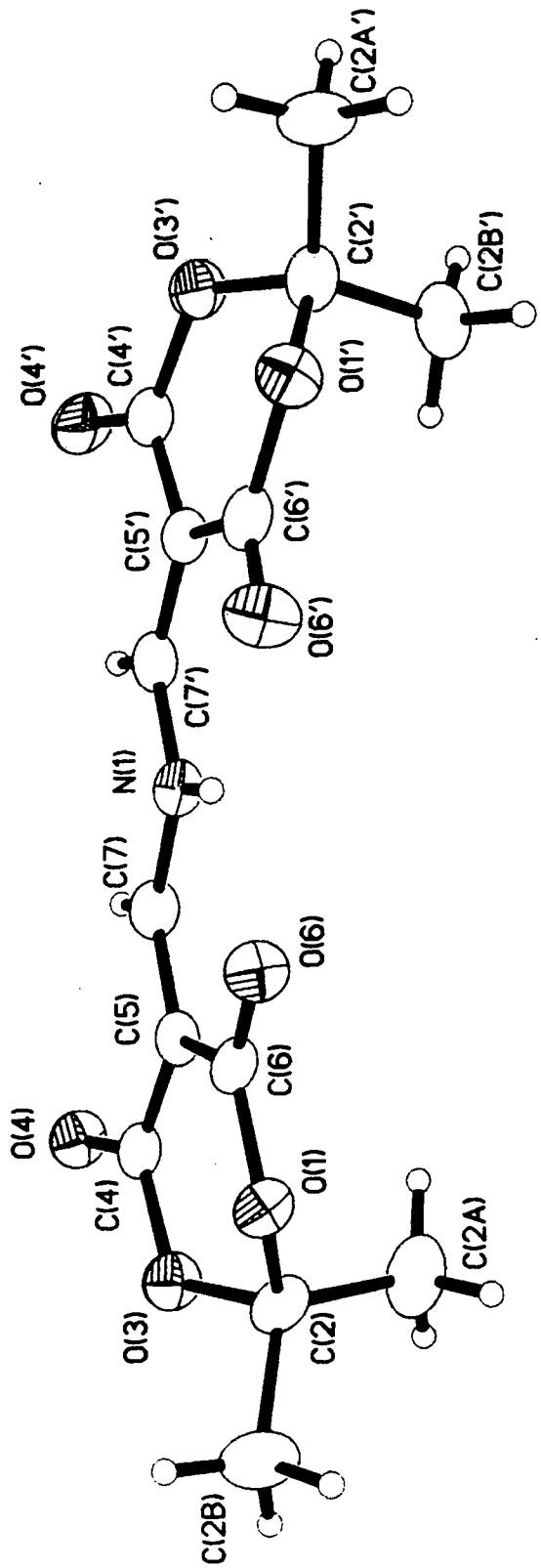
The structure of the reaction product was confirmed by X-ray crystallography[123] and is illustrated in **Scheme 33**, with associated data in **Tables 14, 15** and **16**.

Comparison of bond lengths with the aminomethylidene derivative **160**[123] illustrates the effect of two methylidene Meldrum's acid systems on the molecule.



160

Delocalisation of the N(1) lone pair through the two systems is reflected in the much longer N(1)-C(7)/(7′) bond lengths [average 1.362(8) Å] compared with compound **160** [1.281(14) Å]. Correspondingly the C(5)/(5′)-C(7)/(7′) distance in compound **165** [average 1.350(9) Å] shows more double bond character than in **160** [1.409(15)°]. The configuration of the compound about both N(1)-C(7) and N(1)-C(7′) allows intramolecular bifurcated hydrogen bonding of N(1)-H with O(6) and O(6′). In order to accommodate the hydrogen bonding in the system the average bond angle C(6)/(6′)-C(5)/(5′)-C(7)/(7′) [121.6(7) Å] is larger than C(4)/(4′)-C(5)/(5′)-C(7)/(7′) [117.3(7)°]. The conformation of the dioxanedione rings in **165** can be described as both being approximately 30% chair and 70% boat. The molecule is essentially planar (with the exception of C(2), C(2′) and their methyl substituents) with the largest deviation from the mean plane being O(4′) (0.211 Å).


C(2A')
O(3')
C(2')
C(2B')
O(4')
C(4')
O(1')
C(5')
C(6')
O(6')
C(7')
N(1)
C(7)
O(6)
C(5)
C(6)
O(4)
O(1)
C(4)
C(2A)
O(3)
C(2)
C(2B)

Scheme 33

Table 14 - Bond Lengths (Å)

O(1)-C(6)	1.354(7)
O(1)-C(2)	1.442(7)
C(2)-O(3)	1.455(8)
C(2)-C(2B)	1.507(8)
C(2)-C(2A)	1.497(8)
O(3)-C(4)	1.357(7)
C(4)-O(4)	1.202(7)
C(4)-C(5)	1.466(9)
C(5)-C(7)	1.352(9)
C(5)-C(6)	1.477(8)
C(6)-O(6)	1.209(7)
C(7)-N(1)	1.351(8)
O(6)-O(6´)	3.178(7)
N(1)-C(7´)	1.373(8)
O(1´)-C(6´)	1.361(8)
O(1´)-C(2´)	1.438(8)
C(2´)-O(3´)	1.433(8)
C(2´)-C(2A´)	1.506(9)
C(2´)-C(2B´)	1.518(9)
O(3´)-C(4´)	1.359(8)
C(4´)-O(4´)	1.209(8)
C(4´)-C(5´)	1.463(9)
C(5´)-C(7´)	1.347(9)
C(5´)-C(6´)	1.454(9)
C(6´)-O(6´)	1.211(8)

Table 15 - Bond Angles (degrees)

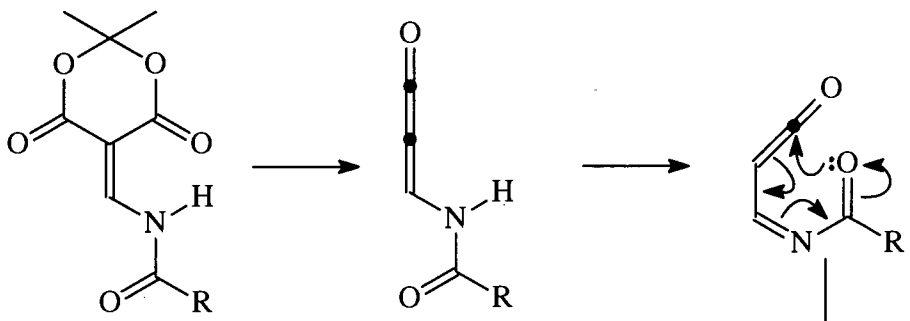
C(6)-O(1)-C(2)	119.6(5)
O(1)-C(2)-O(3)	110.5(5)
O(1)-C(2)-C(2B)	106.1(5)
O(3)-C(2)-C(2B)	105.9(6)
O(1)-C(2)-C(2A)	109.2(6)
O(3)-C(2)-C(2A)	110.0(5)
C(2B)-C(2)-C(2A)	115.1(6)
C(4)-O(3)-C(2)	119.4(6)
O(4)-C(4)-O(3)	117.9(7)
O(4)-C(4)-C(5)	126.3(7)
O(3)-C(4)-C(5)	115.6(7)
C(7)-C(5)-C(4)	116.9(7)
C(7)-C(5)-C(6)	121.8(7)
C(4)-C(5)-C(6)	121.2(7)
O(6)-C(6)-O(1)	118.7(7)
O(6)-C(6)-C(5)	125.1(7)
O(1)-C(6)-C(5)	116.1(7)
C(6)-O(6)-O(6´)	140.0(5)
N(1)-C(7)-C(5)	125.0(7)
C(7)-N(1)-C(7´)	124.7(6)
C(6´)-O(1´)-C(2´)	118.4(6)
O(3´)-C(2´)-O(1´)	111.0(6)
O(3´)-C(2´)-C(2A´)	106.3(6)
O(1´)-C(2´)-C(2A´)	106.7(6)
O(3´)-C(2´)-C(2B´)	109.7(6)
O(1´)-C(2´)-C(2B´)	108.5(6)
C(2´)-C(2A´)-C(2B´)	114.6(7)
C(4´)-O(3´)-C(2´)	119.1(6)
O(4´)-C(4´)-O(3´)	119.0(7)
O(4´)-C(4´)-C(5´)	125.4(8)
O(3´)-C(4´)-C(5´)	115.5(7)
C(7´)-C(5´)-C(6´)	121.4(6)
C(7´)-C(5´)-C(4´)	117.6(7)
C(6´)-C(5´)-C(4´)	120.9(7)
O(6´)-C(6´)-O(1´)	118.7(7)
O(6´)-C(6´)-C(5´)	125.6(8)
O(1´)-C(6´)-C(5´)	115.6(7)
C(6´)-O(6´)-O(6)	139.2(5)
C(5´)-C(7´)-N(1)	124.8(7)

Table 16 - Torsion Angles (degrees)

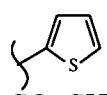
C(6)-O(1)-C(2)-C(3)	-45.7(8)	C(2)-O(1)-C(6)-O(6)	-161.0(6)
C(6)-O(1)-C(2)-C(2A)	75.5(8)	C(2)-O(1)-C(6)-C(5)	20.6(9)
C(6)-O(1)-C(2)-C(2B)	-160.0(6)	C(7)-C(5)-C(6)-O(6)	5.7(11)
O(1)-C(2)-O(3)-C(4)	45.6(8)	C(4)-C(5)-C(6)-O(6)	-171.0(7)
C(2A)-C(2)-O(3)-C(4)	-75.0(8)	C(7)-C(5)-C(6)-O(1)	-176.0(7)
C(2B)-C(2)-O(3)-C(4)	160.0(6)	C(4)-C(5)-C(6)-O(1)	7.3(10)
C(2)-O(3)-C(4)-O(4)	164.9(6)	O(1)-C(6)-O(6)-O(6´)	172.0(4)
C(2)-O(3)-C(4)-C(5)	-20.5(9)	C(5)-C(6)-O(6)-O(6´)	-9.7(12)
O(4)-C(4)-C(5)-C(7)	-10.0(12)	C(6)-C(5)-C(7)-N(1)	-0.3(11)
O(3)-C(4)-C(5)-C(7)	175.9(6)	C(4)-C(5)-C(7)-N(1)	176.6(7)
O(4)-C(4)-C(5)-C(6)	166.9(7)	C(5)-C(7)-N(1)-C(7´)	-180.0(7)
O(3)-C(4)-C(5)-C(6)	-7.2(10)	C(6´)-O(1´)-C(2´)-O(3´)	48.7(8)
C(6´)-O(1´)-C(2´)-C(2A´)	164.1(7)	C(6´)-O(1´)-C(2´)-C(2B´)	-71.9(8)
O(1´)-C(2´)-O(3´)-C(4´)	-47.0(8)	C(2A´)-C(2´)-O(3´)-C(4´)	-162.7(6)
C(2B´)-C(2´)-O(3´)-C(4´)	72.9(8)	C(2´)-O(3´)-C(4´)-O(4´)	-164.9(7)
C(2´)-O(3´)-C(4´)-C(5´)	18.6(10)	O(4´)-C(4´)-C(5´)-C(7´)	11.3(12)
O(3´)-C(4´)-C(5´)-C(7´)	-172.4(7)	O(4´)-C(4´)-C(5´)-C(6´)	-165.8(8)
O(3´)-C(4´)-C(5´)-C(6´)	10.5(10)	C(2´)-O(1´)-C(6´)-O(6´)	161.7(7)
C(2´)-O(1´)-C(6´)-C(5´)	-21.7(9)	C(7´)-C(5´)-C(6´)-O(6´)	-9.4(12)
C(4´)-C(5´)-C(6´)-O(6´)	167.6(8)	C(7´)-C(5´)-C(6´)-O(1´)	174.2(7)
C(4´)-C(5´)-C(6´)-O(1´)	-8.8(10)	O(1´)-C(6´)-O(6´)-O(6)	-167.2(4)
C(5´)-C(6´)-O(6´)-O(6)	16.5(13)	C(6)-O(6)-O(6´)-C(6´)	-3.7(12)
C(6´)-C(5´)-C(7´)-N(1)	-1.0(11)	C(4´)-C(5´)-C(7´)-N(1)	-178.1(7)
C(7)-N(1)-C(7´)-C(5´)	-176.8(7)		

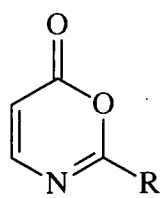
2. Preparation of 2-Substituted-6*H*-1,3-Oxazin-6-ones[118]

The amidomethylidene Meldrum's acid derivatives **153a-h** were all subjected to flash vacuum pyrolysis. A standard furnace temperature for pyrolysis of Meldrum's acid derivatives of 650 °C gave very poor results, with polymer predominantly produced. However, lower furnace temperatures of 450-550 °C gave much cleaner reactions and produced the 2-substituted oxazinones **166a-h** *via* the route shown in **Scheme 34**.



153a-h

(**a**) R = CH_3
(**b**) R = CH_2CH_3
(**c**) R = $CH(CH_3)_2$
(**d**) R = $C(CH_3)_3$
(**e**) R = C_6H_5
(**f**) R = 
(**g**) R = CO_2CH_3
(**h**) R = H



166a-h

Scheme 34

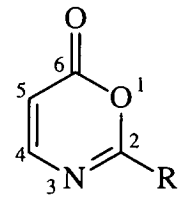
Loss of carbon dioxide and acetone generated the methylideneketene, which underwent a hydrogen shift and cyclisation to give the 2-substituted oxazinones **166a-h** in good yields ranging from 62-80 %.

Previous work in the area of 2-substituted oxazinones has been limited, although a wide range of polysubstituted oxazinones are known.[124] 2-Aryl oxazinones have been previously prepared, initially the 2-phenyl derivative by Steglich and Jendrzejewski[125] in 1981, followed by a range of meta and para substituted 2-aryl compounds by Bernath *et al.*[126] The latter group reported their route to be unsuccessful when the aryl group was replaced by an alkyl group, so limiting its usefulness.

2,4-Disubstituted oxazinones have been prepared previously[127] by liquid-phase thermolysis of appropriately substituted Meldrum's acid derivatives (either in the melt or in solution), but reaction conditions were dependent on substitution patterns and yields were variable, as low as 32%. Consequently, the gas phase method developed is the first general route to 2-substituted oxazinones, applicable across a wide range of substituents, with reliable yields.

The compounds all gave a characteristic pattern in their ^{1}H NMR spectrum due to the H4/H5 coupling. These chemical shifts and coupling constants, along with the ^{13}C chemical shifts are illustrated in **Table 17** (with spectra recorded in $CDCl_3$ unless otherwise stated).

The chemical shifts are very consistent across the range of oxazinones prepared. Position C(4) is the electron poor site and C(5) the electron rich site and this is reflected in the δ values of these carbon atoms. The chemical shift of C(2) varies according to the nature of the substituent, from alkyl to aryl to electron-withdrawing.



166

Table 17

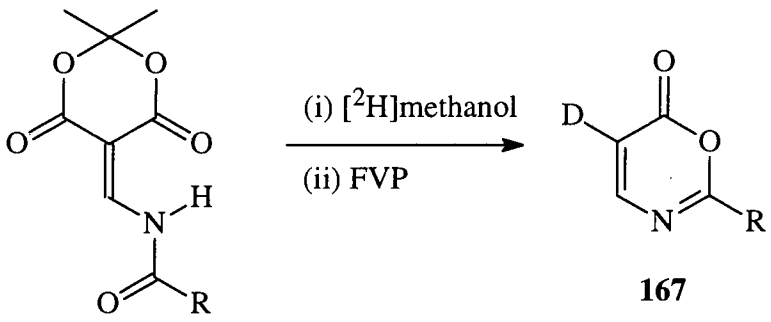
Compound	Chemical Shift (p.p.m.)						^3J (Hz)
166	C(2)	C(4)	C(5)	C(6)	H(4)	H(5)	H(4)/H(5)
a	168.31	153.83	109.39	158.39	7.55	6.09	6.8
b	171.79	153.58	109.23	158.23	7.53	6.03	6.8
c	174.80	153.82	109.35	158.53	7.58	6.06	6.9
d	176.70	153.89	109.31	158.80	7.64	6.10	6.8
e	164.46	154.44	109.28	158.08	7.78	6.18	6.7
f	160.98	154.75	108.36	157.60	7.71	6.10	6.8
g*	157.66/ 157.02	153.69	114.50	157.66/ 157.02	7.98	6.66	6.8
h	156.72	152.90	113.06	156.71	7.63	6.28	7.0

* $[^2H_6]$DMSO

Subjecting the oxazinones to electron impact mass spectrometry produced rather weak molecular ion peaks with a characteristic loss of *m/z* 28 (corresponding to CO). Most of the compounds also gave significant peaks at *m/z* 96 due to loss of the 2-substituent from the ring system.

Two deuteriated oxazinones **167a** and **167b**, specifically labelled in the 5-position, were also prepared. The amidomethylidene Meldrum's acid compounds **153a** and **153b** were dissolved in hot [^{2}H]methanol to exchange the proton on the nitrogen atom for deuterium. The solvent was removed after allowing the solution to stand for 15 min and the crude, deuteriated derivatives pyrolysed under standard conditions. Spectroscopic examination of the oxazinones produced (**167a** and **167b**) showed deuterium atoms exclusively at the 5-positions; this confirmed the mechanism for

formation shown earlier in **Scheme 34**, specifically the hydrogen transfer step producing the acyliminoketene intermediate.



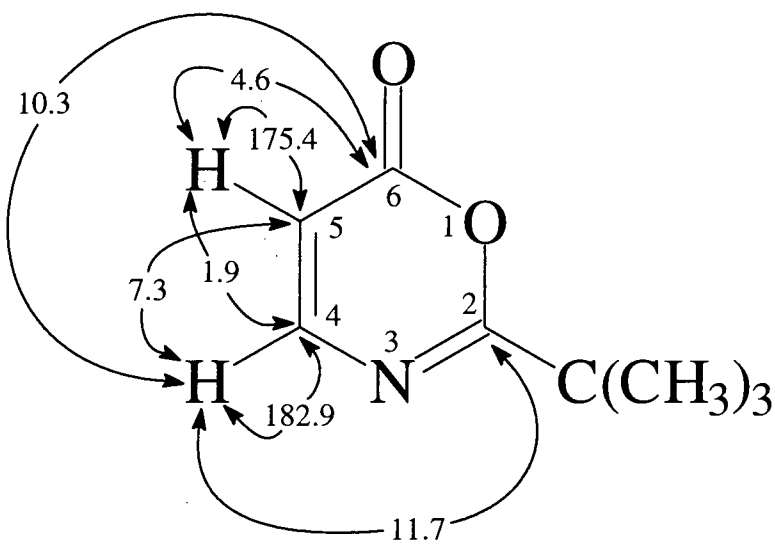
153

(**a**) R = CH_3
(**h**) R = H

167

(**a**) R = CH_3
(**b**) R = H

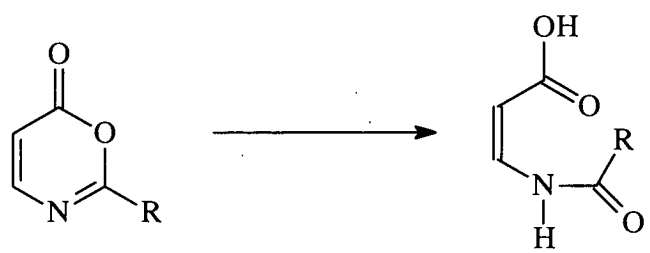
The *t*-butyl derivative **166d** was used to determine the major proton-carbon coupling parameters and these are illustrated in **Scheme 35**.



Scheme 35

C(5) and C(4) appeared as doublets of doublets due to one bond and two bond couplings. The quaternary centre C(6) also showed two couplings of 10.3 and 4.6 Hz; examination of the fully coupled spectrum of the deuterium labelled compound **167a** showed the major interaction to be a three bond coupling with H(4), and the minor to be a two bond coupling with H(5). Quaternary centre C(2) showed a complex pattern due to coupling with the *t*-butyl substituent, but the interaction with H(4) could be assigned as 11.7 Hz, again with the information from **167a**.

All of the 2-alkyl oxazinones produced were oils, and proved to be susceptible to slow hydrolysis to the open chain compound **168**; this was consistent with data reported for the parent compound[128] (R = H).



166 **168**

After two weeks in [^{2}H]chloroform at room temperature compound **166a**, (R = CH_3) was 12% hydrolysed to the open chain compound, which was identified by its characteristic enamide protons at ~5.1 p.p.m. (^3J 9.0 Hz) and ~7.5 p.p.m. (^3J 9.0 and 11.5 Hz).

Although this work utilising primary amides did not produce Meldrum's acid derivatives suitable for pyrrolone production, it provided an insight into the reactivity of amides as *N*-nucleophiles and a new route into 2-substituted oxazinones, which are themselves valuable reagents in heterocyclic chemistry.

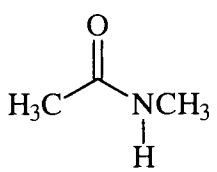
C. REACTIONS OF SECONDARY AMIDES AND UREAS WITH 5-METHOXYMETHYLIDENE MELDRUM'S ACID

Following the success of reactions with primary amides as detailed in the previous chapter, the methodology was extended to secondary amides, acyclic and cyclic, both being potential precursors for the formation of *N*-protected pyrrolones *via* FVP of their amidomethylidene Meldrum's acid derivatives.

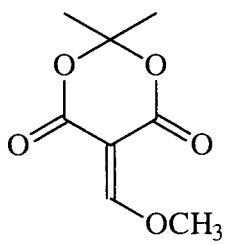
1. Secondary, Acyclic Amides and Ureas

(a) Reactions With 5-Methoxymethylidene Meldrum's Acid

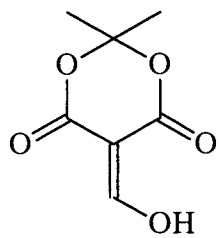
The secondary amide *N*-methylacetamide **169** was reacted with 5-methoxy-methylidene Meldrum's acid **89**. Reactions at room temperature in acetonitrile failed to give anything but unreacted starting materials.



169



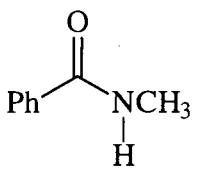
89



154

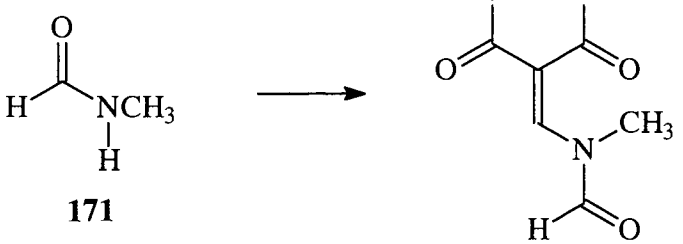
Refluxing the reaction mixture for prolonged periods of time (up to 3 days) also failed to produce any reaction, other than converting compound **89** to 5-hydroxymethylidene Meldrum's acid **154**, which was isolated by dry flash column chromatography. Repeating this reaction with *N*-methylbenzamide **170** gave the same results as with *N*-methylacetamide, with unreacted amide being recovered after

prolonged reaction times. This lack of reactivity may be due to the nitrogen atom being more sterically hindered than in primary amides, predominantly due to the nitrogen atom substituent, but also from the additive effect of the substituent on the carbonyl carbon atom.



170

However, *N*-methylformamide **171** the simplest secondary acyclic amide, did react with 5-methoxymethylidene Meldrum's acid. After heating the reaction mixture under reflux for 17 h the crude product was examined by ^{1}H NMR spectroscopy; very surprisingly (in the context of the two previous experiments) it was shown to be the desired aminomethylidene Meldrum's acid derivative **172**. The product was isolated in a moderate yield of 57%. This reaction may have proceeded successfully, where previous examples have failed, as this secondary acyclic amide **171** has the minimum amount of steric hindrance for this type of compound (with only a methyl substituent on the nitrogen atom).

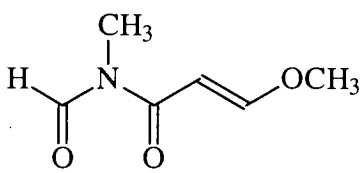


171 **172**

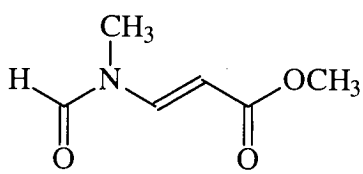
The reaction time was extended past 17 h, in an attempt to increase this moderate yield. As the reaction proceeded it was monitored by ^{1}H NMR spectroscopy; this was done by removing small aliquots of the reaction mixture at various time intervals, removing the solvent from the aliquot under reduced pressure and examining the residue by ^{1}H NMR spectroscopy.

Such monitoring indicated that a secondary reaction was taking place. The characteristic methine proton signal and the singlet due to the Meldrum's ring methyl groups from the aminomethylidene derivative **172** slowly disappeared. At the same time, two sets of alkene-type doublets appeared at 7.6 p.p.m. and 5.36 p.p.m., both with large coupling constants of 13.5 Hz. After a reaction time of 75 h, no further change in the ^{1}H NMR spectrum was observed, and the reaction worked-up. A single product was isolated, but in a very low yield of 11%.

Further examination of the recrystallised product by ^{1}H and ^{13}C NMR spectroscopy and electron impact mass spectrometry provided enough data to assign two possible structures, **173** and **174a** to the compound.



173

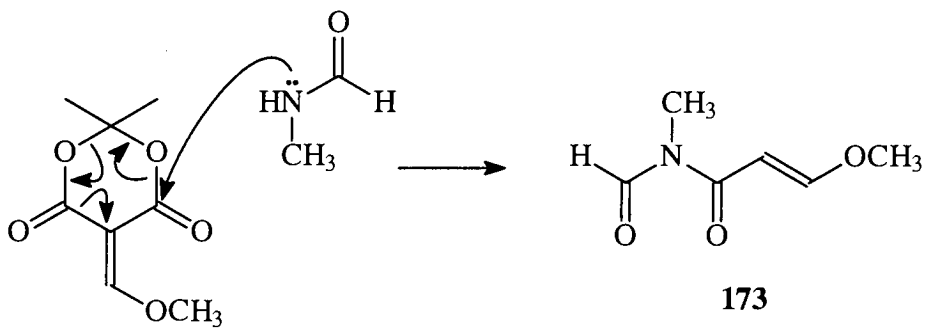


174a

Scheme 36 illustrates how these two compounds could have been formed during the reaction. In **Route A**, the amide attacks directly at the carbonyl carbon atom of the Meldrum's acid ring to produce compound **173**. In **Route B**, the amide attacks at the methine carbon to produce the desired product **172** and methanol as a by-product.

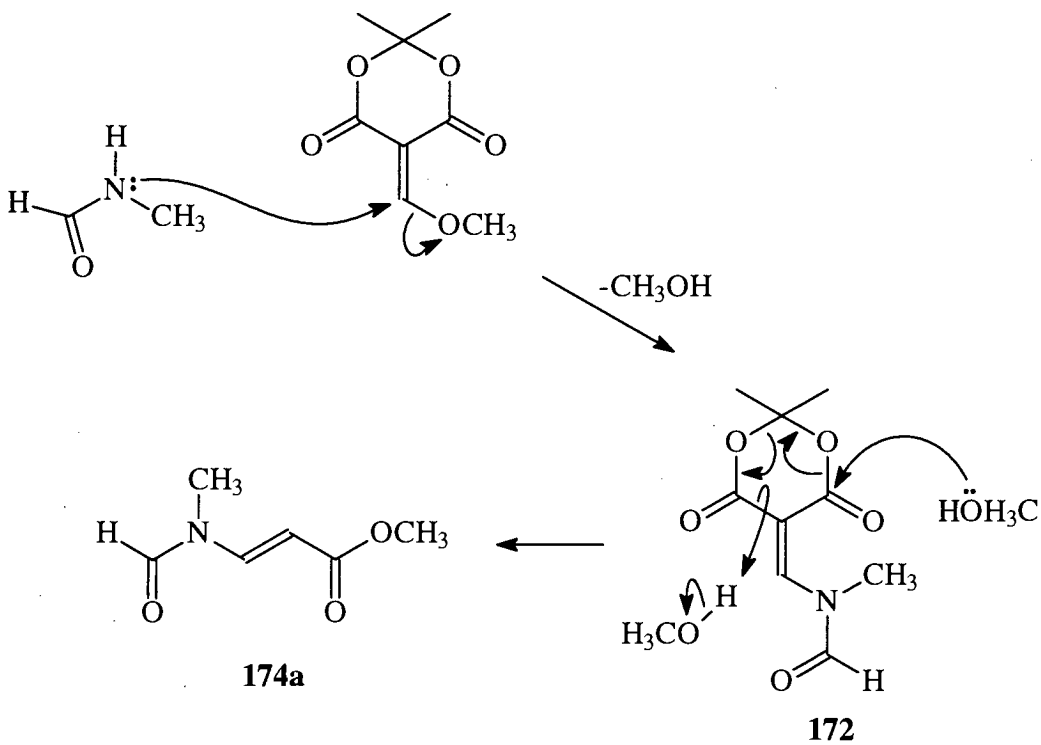
The small amount of methanol produced can go on to attack at the carbonyl carbon atom of the Meldrum's acid ring, causing ring opening to occur and compound **174a** to be formed.

Route A



173

Route B



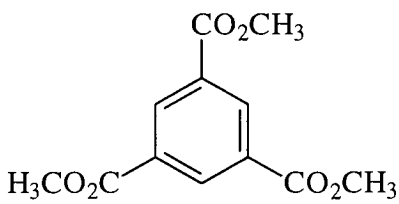
174a **172**

Scheme 36

The absolute assignment of the reaction product was determined by an X-ray crystal structure of a related compound (see page 128), showing the correct structure to be **174a**, formed *via* **Route B**.

This result was rather unexpected considering the very small amount of methanol that would be present in the solution during the reaction and the length of time this relatively volatile compound would have to remain in a mixture heated under reflux for 75 h. These factors are reflected in the product yield; compound **174a** was isolated in a yield of only 11% after dry flash column chromatography.

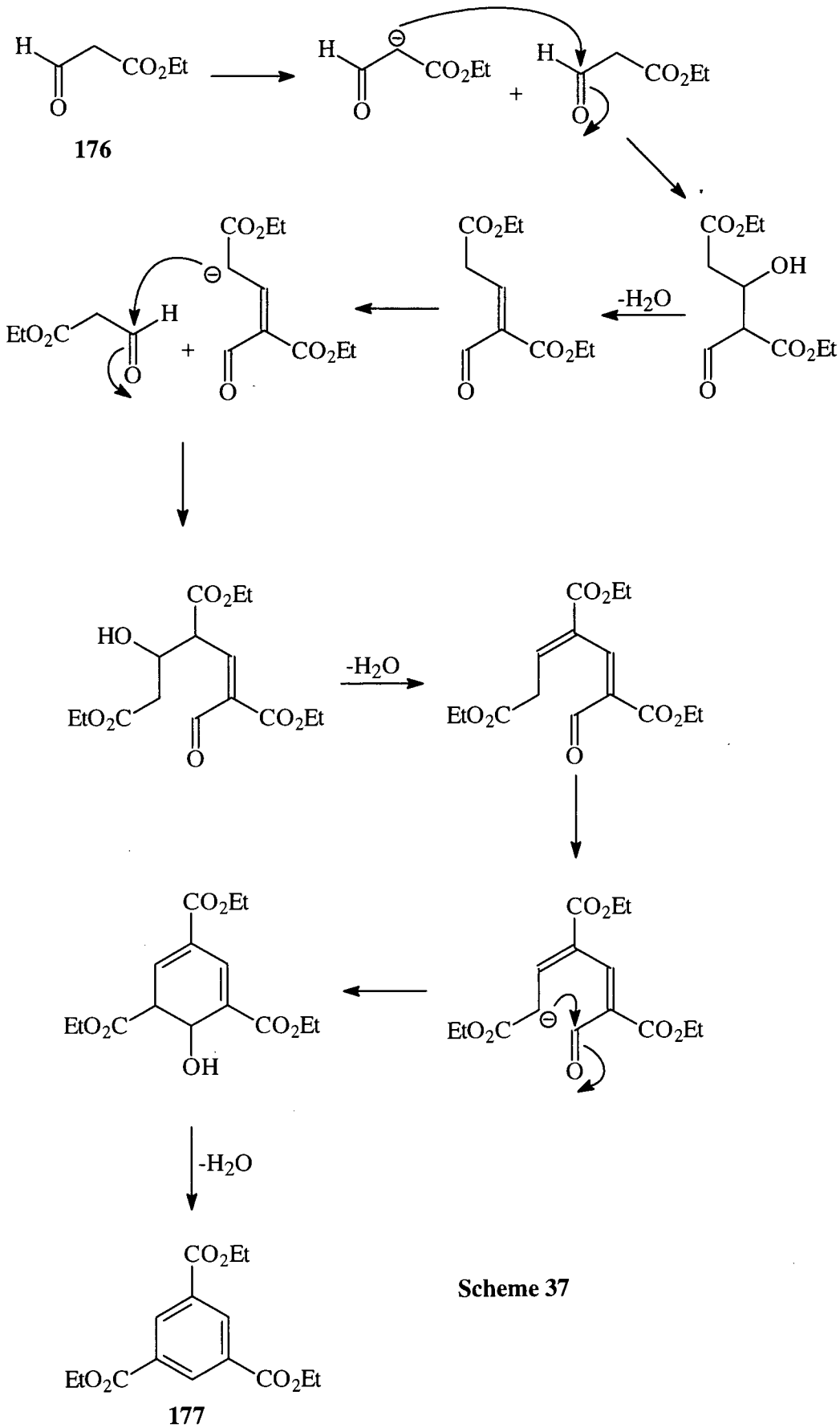
A second product was also isolated from the column, and shown by NMR and mass spectrometry to be trimethyl 1,3,5-benzenetricarboxylate **175**.



175

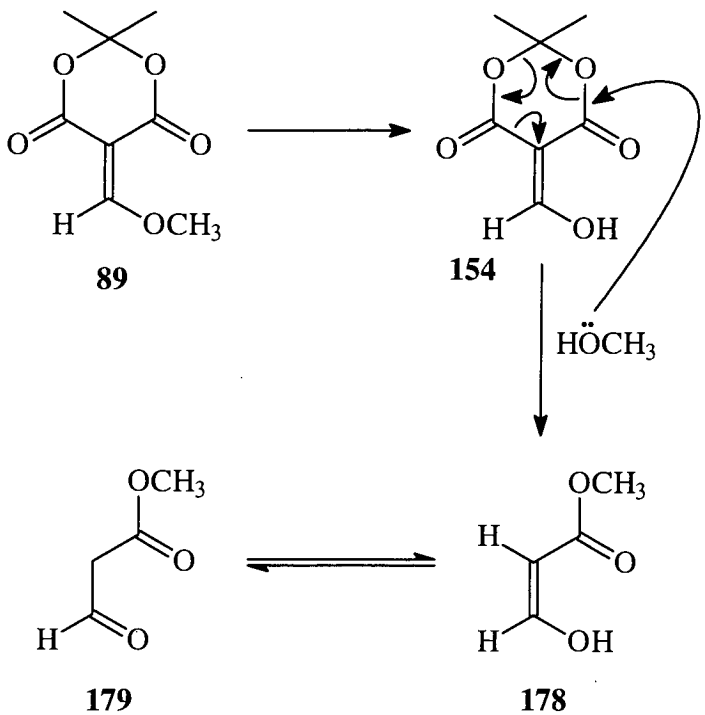
A very early publication by von Pechmann in 1892[129] described how triethyl 1,3,5-benzenetricarboxylate **177** was produced from ethyl formylacetate **176**, the mechanism of which is shown in **Scheme 37**.

In this scheme three molecules of the precursor trimerise to form the benzene derivative **177**. Changing the precursor ethyl ester to a methyl ester should have no effect on the reaction path as illustrated, so the desired trimethyl compound isolated could also be formed by this route.



Scheme 37

Examining 5-methoxymethylidene Meldrum's acid **89** more closely shows how the necessary precursor to the tricarboxylate could be produced, as illustrated in **Scheme 38**.



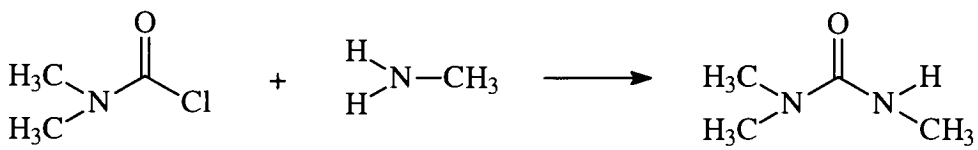
Scheme 38

As discussed previously, hydrolysis of 5-methoxymethylidene Meldrum's acid to the corresponding hydroxy derivative **154** occurs relatively easily when the compound is exposed to air for prolonged periods of time. The methanol by-product of the desired reaction of compound **89** with the amide can then attack the Meldrum's acid ring to generate the vinyl alcohol **178** which can tautomerise to the required aldehyde **179**. This molecule can then go on to trimerise to produce the tricarboxylate derivative **175** isolated.

In view of the poor reactivity of the secondary amides, alternative compounds were sought which had similar features, but with a more reactive nitrogen atom within the

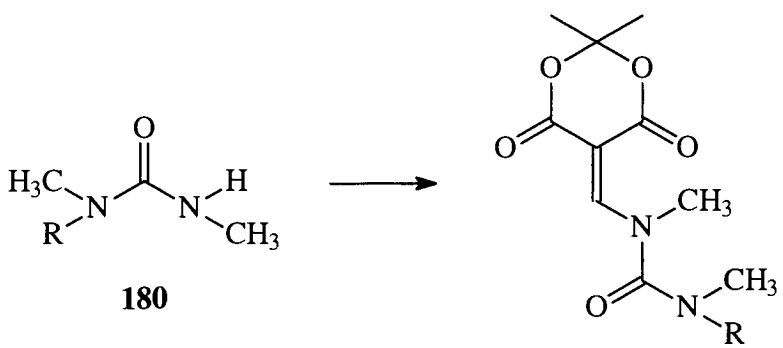
molecule. These requirements pointed to ureas; as there are two nitrogen atoms within this type of compound either or both can donate their lone pairs into the carbonyl group and consequently the nitrogen atoms are more electron rich and so more nucleophilic in character.

Two secondary, acyclic ureas *N,N′*-dimethylurea **180a** and *N,N,N′*-trimethylurea **180b** were successfully reacted with 5-methoxymethylidene Meldrum's acid. *N,N,N′*-Trimethylurea[130,131] **180b** was prepared from dimethylcarbamoyl chloride **181** and methylamine **182**.



181 **182** **180b**

In agreement with the reasoning above, the reaction of *N,N′*-dimethylurea **180a** successfully produced the aminomethylidene derivative **183a** (in a yield of 48%), but *N,N,N′*-trimethylurea gave only a 10% yield of derivative **183b** after dry flash column chromatography.



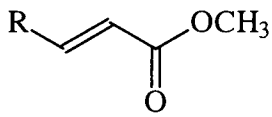
180

(**a**) R = H
(**b**) R = CH_3

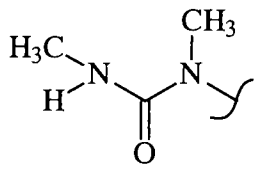
183

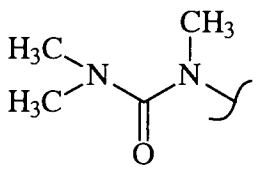
(**a**) R = H
(**b**) R = CH_3

Extending the reflux time of the two reactions had the same effect as with *N*-methylformamide, and produced compounds **174b** and **174c**, although the latter in a yield of only 8%. Both reactions also produced trimethyl 1,3,5-benzene-tricarboxylate.



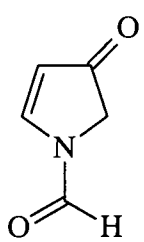
174

(**b**) R = 

(**c**) R = 

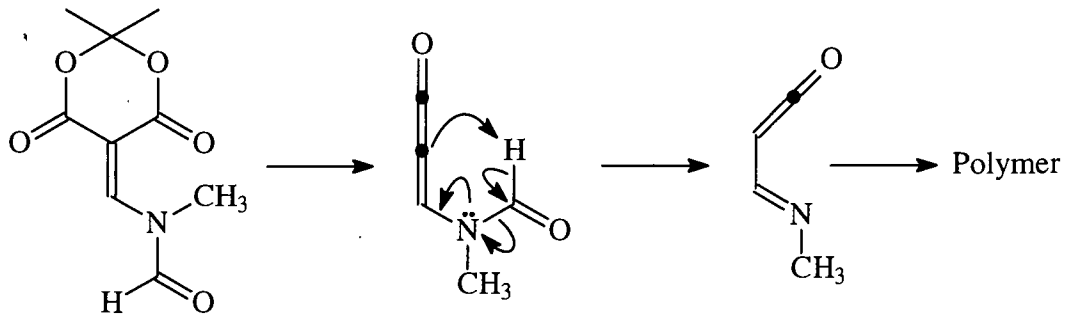
(b) Pyrolyses of Meldrum's Acid Derivatives Produced From Secondary Acyclic Amides and Ureas

The three derivatives prepared were then subjected to flash vacuum pyrolysis. Pyrolysis of compound **172** could theoretically be expected to produce pyrrolone **184a**, but FVP over a range of temperatures (500-700 °C) gave no identifiable products on examination by ^{1}H NMR spectroscopy.



184a

Closer examination of the reaction pathway, shown in **Scheme 39**, revealed an alternative hydrogen shift that could have occurred during pyrolysis.

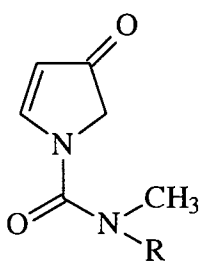


172 **185** **186**

Scheme 39

Loss of acetone and carbon dioxide upon collapse of the Meldrum's acid ring produces, as expected, the methylideneketene **185**. However, instead of the hydrogen shift occurring from a hydrogen atom in the methyl group, the formamido proton is abstracted, leading to an intermediate **186** which then polymerises.

Pyrolysis of the Meldrum's acid derivatives produced from the ureas could be expected to produce the pyrrolones **187a** and **187b**.



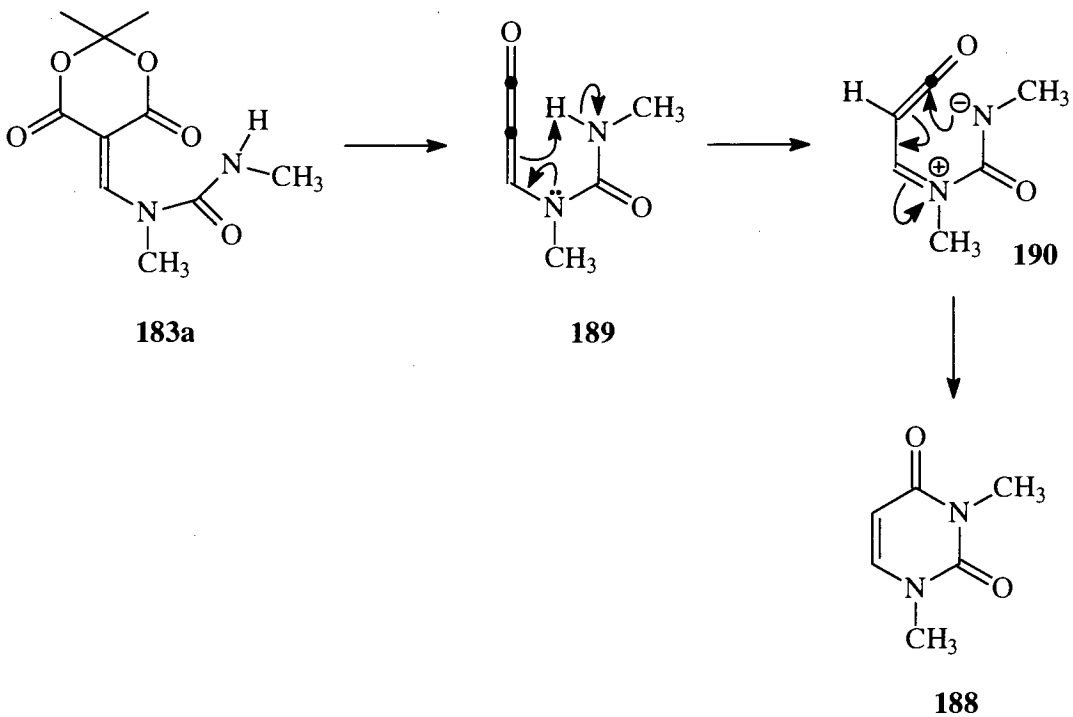
(**a**) R = H
(**b**) R = CH_3

187

However, pyrolysis of the trimethylurea derivative **183b** produced mainly insoluble brown polymer with no identifiable products in the very minor, soluble portion of the

pyrolysate. Pyrolysis of the dimethylurea derivative **183a** produced a dark brown pyrolysate which was removed from the FVP trap with hot acetone. A dark brown solid slowly precipitated from this solution and was collected by filtration. Examination by ^{1}H NMR spectroscopy showed it to be *N,N'*-dimethyluracil **188**, (11%) which was produced by the route illustrated in **Scheme 40**.

The methylideneketene **189** produced by pyrolysis of compound **183a** underwent an alternative hydrogen shift to the one expected; the hydrogen atom attached to the NCH_3 group shifted, rather than a hydrogen atom from the methyl group on the other nitrogen atom. The intermediate formed (**190**) has a negative charge on the nitrogen atom, and this can be delocalised into the adjacent carbonyl group, providing extra stability. Cyclisation of the intermediate produced the disubstituted uracil **188**.



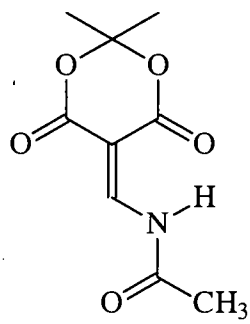
183a **189** **190** **188**

Scheme 40

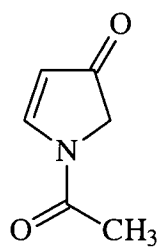
The Meldrum's acid derivative produced from trimethylurea cannot undergo this alternative hydrogen shift (to produce a uracil) as the compound is dimethylated and is missing the necessary hydrogen atom. However, it is unclear why pyrrolone formation did not occur during the pyrolysis and why only polymer was produced.

Due to the poor reactivity of secondary acyclic amides with 5-methoxymethylidene Meldrum's acid, an alternative approach was sought into the required Meldrum's acid derivatives.

A number of attempts were made to methylate the amidomethylidene Meldrum's acid derivative **153a** (prepared as described in the previous chapter) on the nitrogen atom. Successful methylation and FVP could then produce the desired pyrrolone **184b**.



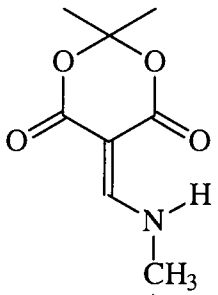
153a



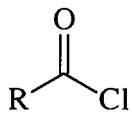
184b

Methylation[90] using a combination of sodium hydride and methyl iodide in dimethylsulfoxide at room temperature proved unsuccessful, even after a 96 h reaction; starting material was always quantitatively recovered. Changing the hard methylating agent to the softer methylating agent methyl *p*-toluenesulfonate, and heating the reaction mixture to 90 °C had no effect. Hünig's base was also tried as an alternative to sodium hydride, as this bulky organic base would not be able to chelate in a cavity in the starting material (as is possible with a sodium ion), but this was also unsuccessful.

An alternative route to compound **153a** would be to start with the methyl group in place and add the acyl substituent. Following the failure to methylate the *N*-amido derivative, attempts were made to acylate 5-(*N*-methylaminomethylidene) Meldrum's acid **160**.[90]



160

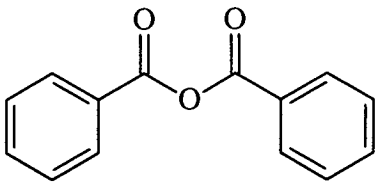


158

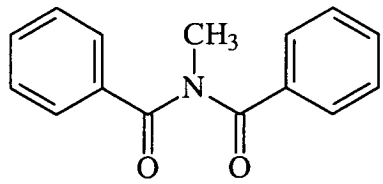
(**c**) R = CH_3
(**d**) R = C_6H_5

However, acylation using acetyl chloride **158c** and triethylamine, with a reaction time of 96 h in refluxing acetonitrile gave only unreacted starting material. The extended reflux times may have boiled off the highly volatile acetyl chloride so the acylating agent was changed to the less volatile benzoyl chloride **158d**. However, reaction with one equivalent of benzoyl chloride and a reflux time of 24 h also gave unreacted Meldrum's acid derivative. Using benzoyl chloride as the reaction solvent proved too harsh, and resulted only in decomposition. However, a reaction with five equivalents of benzoyl chloride, with a reflux time of 5 days gave a number of products; thin layer chromatography and ^{1}H NMR spectroscopy of the mixture indicated that none were unreacted starting material. The mixture was subjected to dry flash column chromatography and three compounds were isolated and identified.

The first compound isolated was identified as benzoic anhydride **191**, a by-product from the benzoyl chloride.



191



192

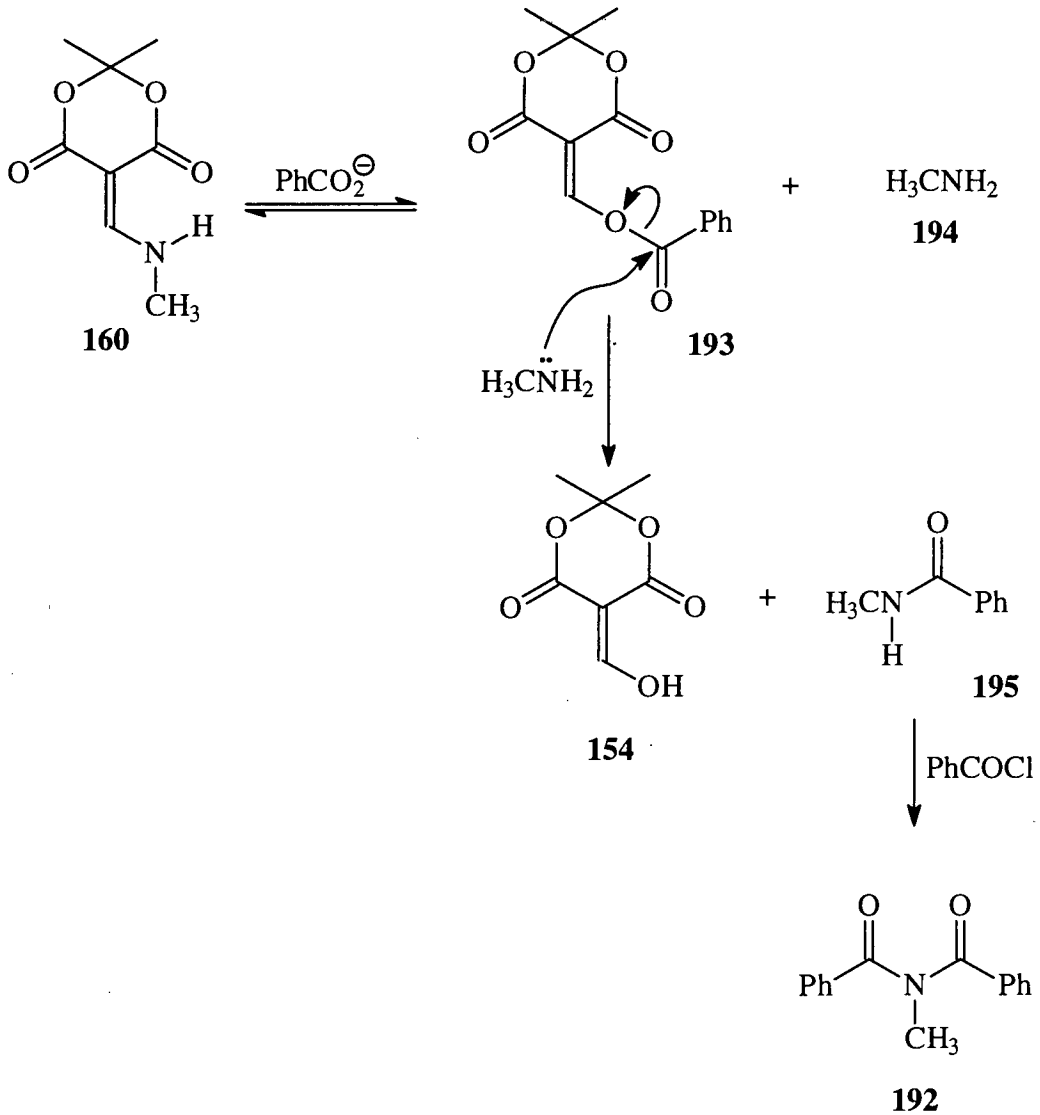
The second and third compounds were isolated as a mixture. Examination by ^{1}H NMR spectroscopy indicated one of the components was benzoic acid, a product of the reaction work-up procedure, so this was separated from the third component *via* a basic extraction. The now pure third component was examined by ^{1}H and ^{13}C NMR spectroscopy and these data, combined with those obtained from the mass spectrum, indicated the third component had the structure **192**, namely *N*-benzoyl-*N*-methylbenzamide. The data obtained were consistent with those reported in the literature[132] for this compound.

This compound contains components of both the aminomethylidene derivative and benzoyl chloride, indicating a reaction was taking place between the two compounds.

Previous work in the literature[133] has shown amides can react with acid chlorides and acid anhydrides to produce imides (and in the latter case nitriles, depending on the substitution patterns of the reactants). Based on this information, a possible mechanism to explain the formation of compound **192** is shown in **Scheme 41**.

In the presence of benzoyl chloride the aminomethylidene derivative **160** can be in equilibrium with compound **193** and methylamine **194**. These two compounds can react together to produce the by-product 5-hydroxymethylidene Meldrum's acid **154**, but more importantly, the amide **195**; this amide can go on to react with benzoyl chloride (present in excess) as described in the literature[133] to produce the imide **192**.

The by-product **154** was not isolated, but it is not unusual for Meldrum's acid derivatives to decompose during dry flash column chromatography and the imide **192** was isolated in a yield of only 30%; this poor recovery of materials is perhaps a reflection on the harsh conditions employed in this reaction.

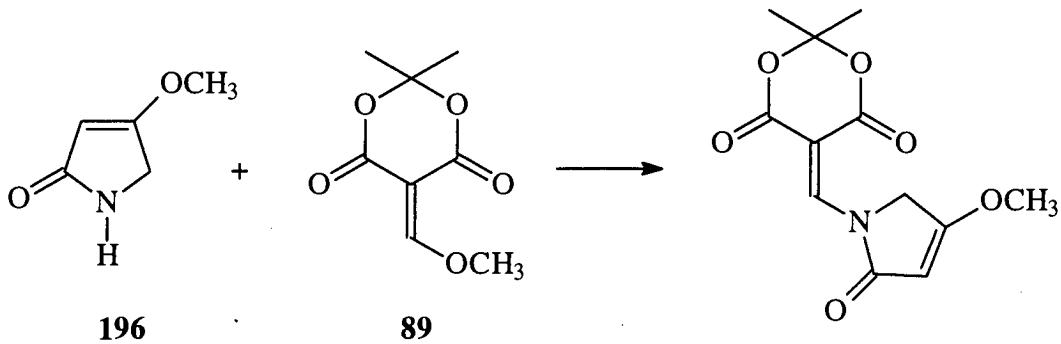


Scheme 41

Due to this alternative reaction taking place, this approach was not continued, and an alternative protecting group was sought.

2. Secondary, Cyclic Amides and Ureas

Previous preliminary work in this area[134] has shown it is possible to react successfully a cyclic, secondary amide with 5-methoxymethylidene Meldrum's acid. 1,5-Dihydro-4-methoxypyrrol-2(2*H*)-one **196** was reacted with 5-methoxy-methylidene Meldrum's acid **89** and produced the amidomethylidene derivative **197**, in an excellent yield of 90%.



196 **89** **197**

This result is in complete contrast to those obtained with secondary, acyclic amides, and can be attributed to features present in the cyclic system that are not present in the acyclic system.

Due to the constraints of the ring (especially in the case of 5-membered rings) in the cyclic amides, any ring substituents are "tied back" from the nitrogen atom, so reducing any steric effects, and increasing the accessibility of the nitrogen atom.

Also in the cyclic system, the conformation of the amide bond is *E*; this conformation is higher in energy than the *Z* conformation, (adopted predominantly by acyclic amides for example as shown in **Scheme 42**[135]) with barriers to rotation in the range 75-92 kJmol^{-1},[136] so making it more reactive.

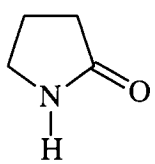
Z (~97%) *E* (~3%)

Scheme 42

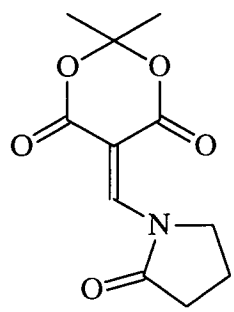
This positive result indicated secondary cyclic amides could ultimately provide a route into the pyrrolone system, so the chemistry of this area was explored.

(a) Reactions With 5-Methoxymethylidene Meldrum's Acid

A simple cyclic amide, pyrrolidin-2-one **198** was reacted with 5-methoxymethylidene Meldrum's acid. An 8 h reflux in acetonitrile gave the desired Meldrum's acid derivative **199a** in a good yield of 74%.



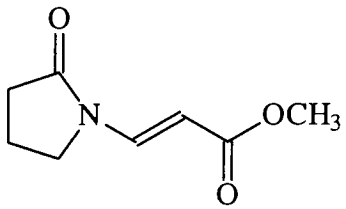
198



199a

Allowing the reflux to continue beyond 8 h, and monitoring the reaction by ^{1}H NMR spectroscopy, showed the appearance of two sets of doublets, as in the case of the secondary, acyclic amides and ureas. The reaction was worked-up after 72 h and the open chain prop-2-enoate **200a** (whose structure was assigned by X-ray

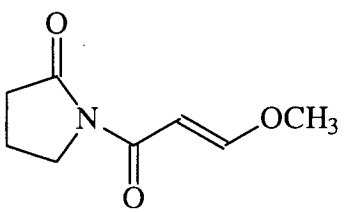
crystallography) was obtained after column chromatography. Trimethyl 1,3,5-benzenetricarboxylate was also isolated, as in the previous reactions reported.



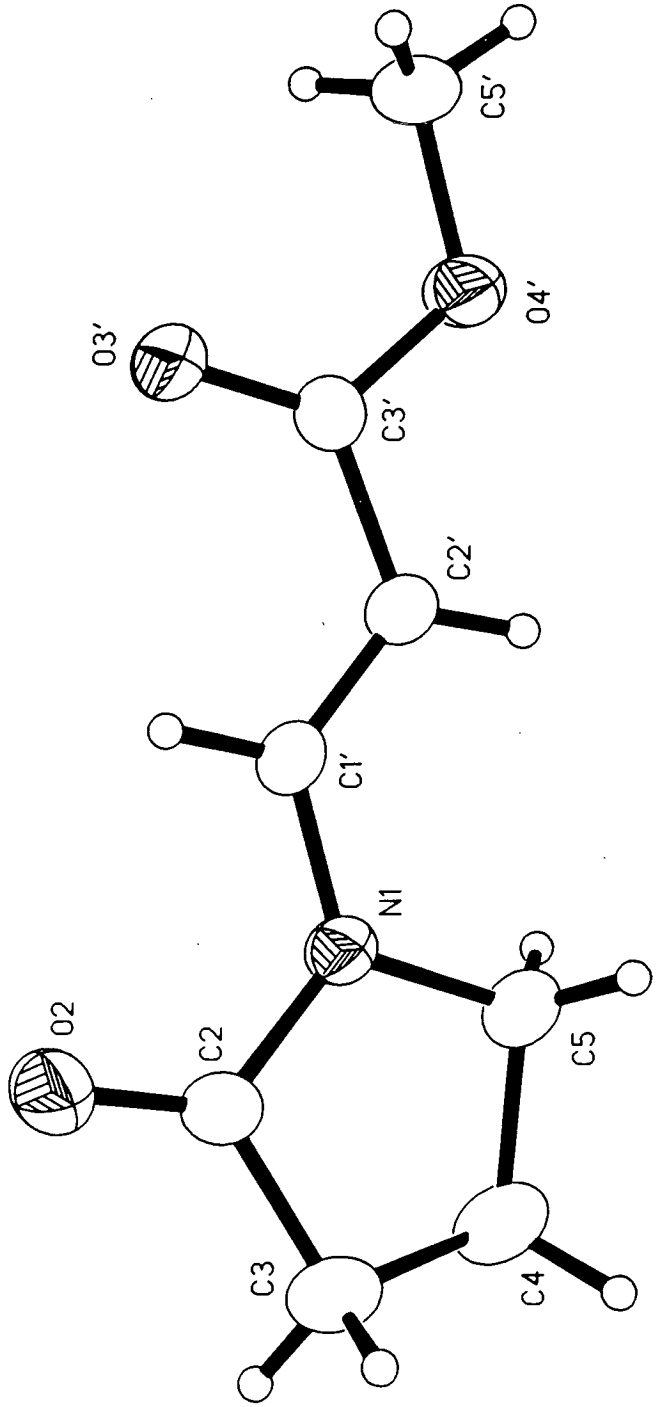
200a

A crystal structure of the prop-2-enoate compound was obtained to determine the absolute connectivity in the compound and other related compounds. This is illustrated in **Scheme 43**, with the relevant bond lengths, bond angles and torsion angles in **Tables 18**, **19** and **20** respectively.

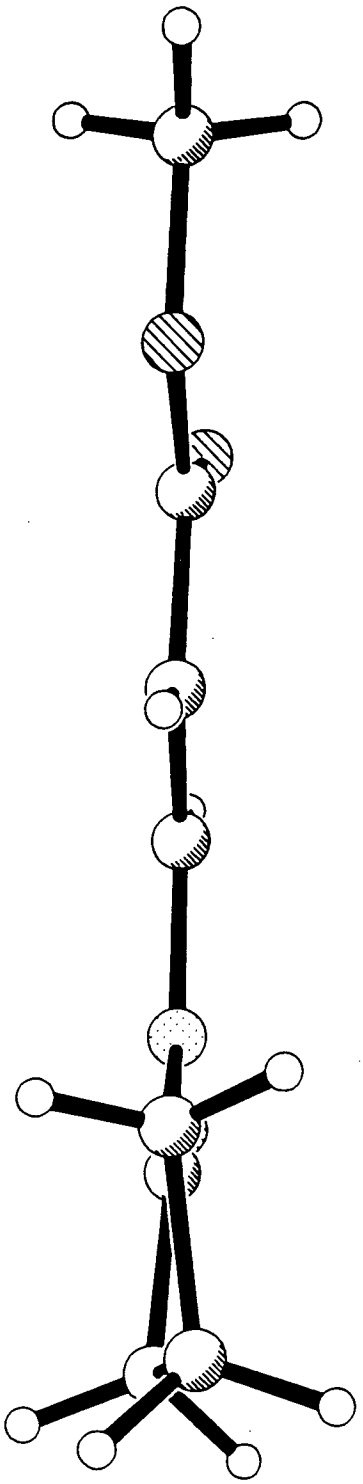
The X-ray analysis confirmed that the prop-2-enoate chain was present as in compound **200a**, not the alternative side chain, as shown in compound **201**. **Scheme 44** shows a side view of the molecule, and illustrates the planarity of the compound.



201



Scheme 43



Scheme 44

Table 18 - Bond Lengths (Å)

N(1)-C(1´)	1.372(4)
N(1)-C(2)	1.383(4)
N(1)-C(5)	1.452(4)
C(2)-O(2)	1.208(4)
C(2)-C(3)	1.489(5)
C(3)-C(4)	1.509(5)
C(4)-C(5)	1.520(5)
C(1´)-C(2´)	1.324(4)
C(2´)-C(3´)	1.456(4)
C(3´)-O(3´)	1.205(4)
C(3´)-O(4´)	1.338(4)
O(4´)-C(5´)	1.449(4)

Table 19 - Bond Angles (degrees)

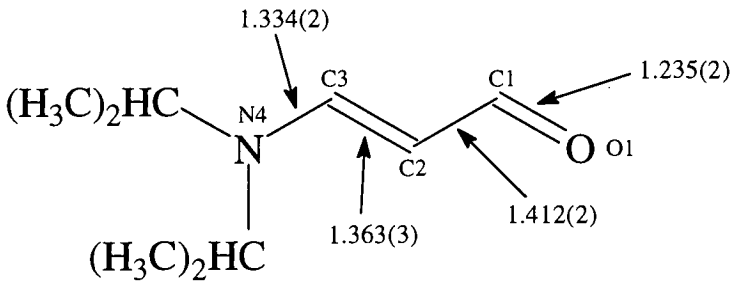
C(1´)-N(1)-C(2)	123.0(3)
C(1´)-N(1)-C(5)	123.4(3)
C(2)-N(1)-C(5)	113.6(3)
O(2)-C(2)-N(1)	123.5(3)
O(2)-C(2)-C(3)	128.6(3)
N(1)-C(2)-C(3)	107.9(3)
C(2)-C(3)-C(4)	105.2(3)
C(3)-C(4)-C(5)	106.3(3)
N(1)-C(5)-C(4)	103.6(3)
C(2´)-C(1´)-N(1)	125.8(3)
C(1´)-C(2´)-C(3´)	120.1(3)
O(3´)-C(3´)-O(4´)	122.7(3)
O(3´)-C(3´)-C(2´)	126.6(3)
O(4´)-C(3´)-C(2´)	110.7(3)
C(3´)-O(4´)-C(5´)	116.7(3)

Table 20 - Torsion Angles (degrees)

C(1´)-N(1)-C(2)-O(2)	3.9(5)
C(5)-N(1)-C(2)-O(2)	-178.4(4)
C(1´)-N(1)-C(2)-C(3)	-174.8(3)
C(5)-N(1)-C(2)-C(3)	2.9(4)
O(2)-C(2)-C(3)-C(4)	167.9(4)
N(1)-C(2)-C(3)-C(4)	-13.4(4)
C(2)-C(3)-C(4)-C(5)	18.6(4)
C(1´)-N(1)-C(5)-C(4)	-173.5(3)
C(2)-N(1)-C(5)-C(4)	8.8(4)
C(3)-C(4)-C(5)-N(1)	-16.6(4)
C(2)-N(1)-C(1´)-C(2´)	175.9(4)
C(5)-N(1)-C(1´)-C(2´)	-1.6(5)
N(1)-C(1´)-C(2´)-C(3´)	178.5(3)
C(1´)-C(2´)-C(3´)-O(3´)	-2.1(6)
C(1´)-C(2´)-C(3´)-O(4´)	178.2(3)
O(3´)-C(3´)-O(4´)-C(5´)	0.6(5)
C(2´)-C(3´)-O(4´)-C(5´)	-179.8(3)

The N(1)-C(2) bond length [1.383(4) Å] in the pyrrolidine ring is significantly shorter than the other four; this is due to the delocalisation of the nitrogen atom lone pair into the ring carbonyl group, giving the N(1)-C(2) bond significant double bond character. The nitrogen atom lone pair can also be delocalised through the chain, and this is reflected in the N(1)-C(1´) bond length [1.372(4) Å] which shows significant double bond character, and the C(1´)-C(2´) bond length [1.324(4) Å] which shows some single bond character.

A related compound in the literature[137] is the enaminal shown in **Scheme 45**, along with selected bond lengths (in Angstroms).

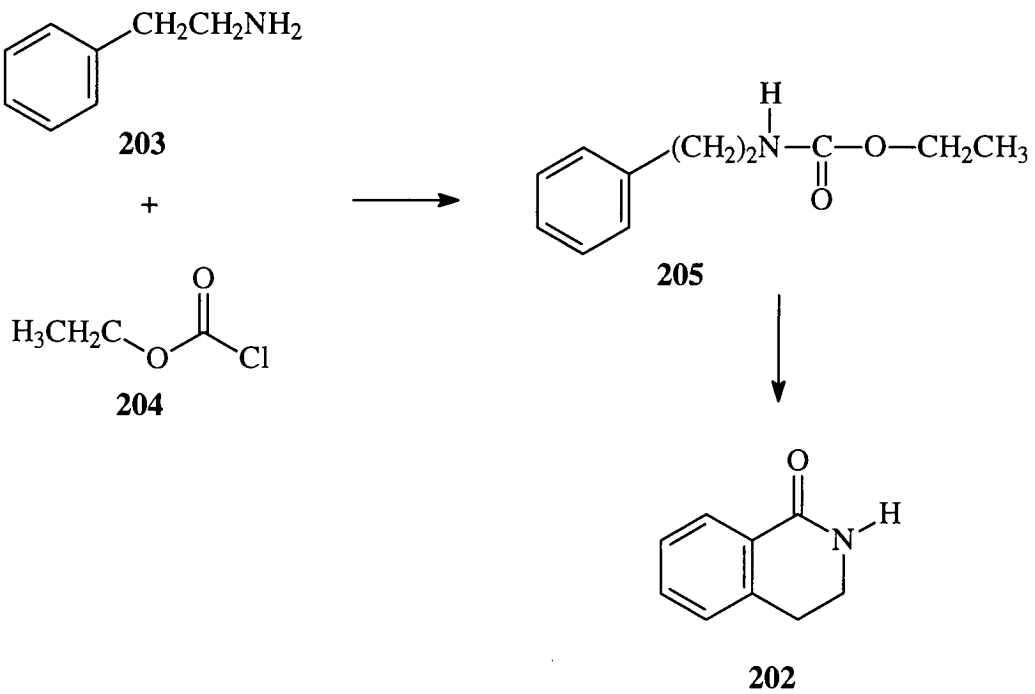


Scheme 45

In this case, delocalisation of the nitrogen atom's lone pair occurs in one direction, not two. Correspondingly, the C(1)-C(2) and C(3)-N(4) bond lengths [1.412(2) Å and 1.334(2) Å respectively] are shorter than in the prop-2-enoate, and the C(2)-C(3) bond length [1.363(3) Å] is longer; the general trend is however the same in both compounds.

Following the success of the pyrrolidin-2-one reaction, a range of cyclic secondary amides were reacted with 5-methoxymethylidene Meldrum's acid, namely 5-methylpyrrolidin-2-one, piperidin-2-one, imidazolidin-2-one, 3,4-dihydro-isoquinolin-1(2*H*)-one and 2,3-dihydroisoindol-1(1*H*)-one.

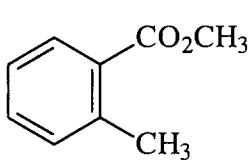
Two of these amides were not commercially available. 3,4-Dihydroisoquinolin-1(2*H*)-one[138] **202** was synthesised in two steps as shown in **Scheme 46**.



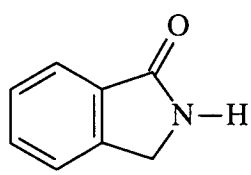
Scheme 46

Ethyl-*N*-(2-phenethyl)carbamate **205** was prepared from 2-phenylethylamine **203** and ethylchloroformate **204** in an excellent yield of 89%. The compound was then cyclised by heating in polyphosphoric acid to give the isoquinolinone **202** in a 61% yield.

2,3-Dihydroisoindol-1(1*H*)-one[139] **207** was prepared from methyl *o*-toluate **206**.



206

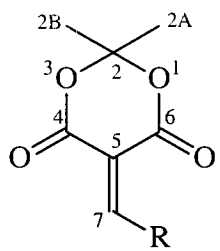


207

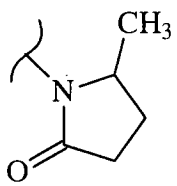
Compound **206** was brominated with *N*-bromosuccinimide in the presence of dibenzoyl peroxide; ammonia gas was bubbled through the resulting reaction mixture whilst being heated under reflux to give the desired, cyclised product in a moderate yield of 41%.

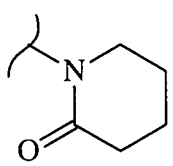
Reactions of these cyclic amides with 5-methoxymethylidene Meldrum's acid were monitored by removing aliquots of the solution at appropriate intervals, and examining them by ^{1}H NMR spectroscopy, looking particularly for the disappearance of the OCH_3 singlet at ~4 p.p.m.

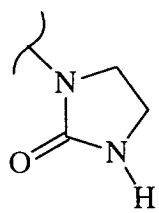
All of the cyclic amides successfully produced Meldrum's acid derivatives **199b-f**. Reflux times were generally between 6 and 8 h, except in the case of 3,4-dihydroisoquinolin-1(2*H*)-one which required an 18 h reaction time to produce **199e**. Yields ranged from 58% (**199d**) to 74% (**199a**).

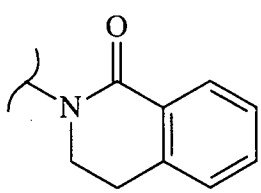


199

(**b**) R = 

(**c**) R = 

(**d**) R = 

(**e**) R = 

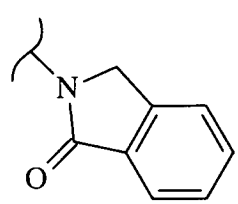
(**f**) R = 

Table 21 shows a selection of ^{1}H and ^{13}C chemical shifts for compounds **199a-f**. All spectra were recorded in [^{2}H]chloroform unless otherwise stated.

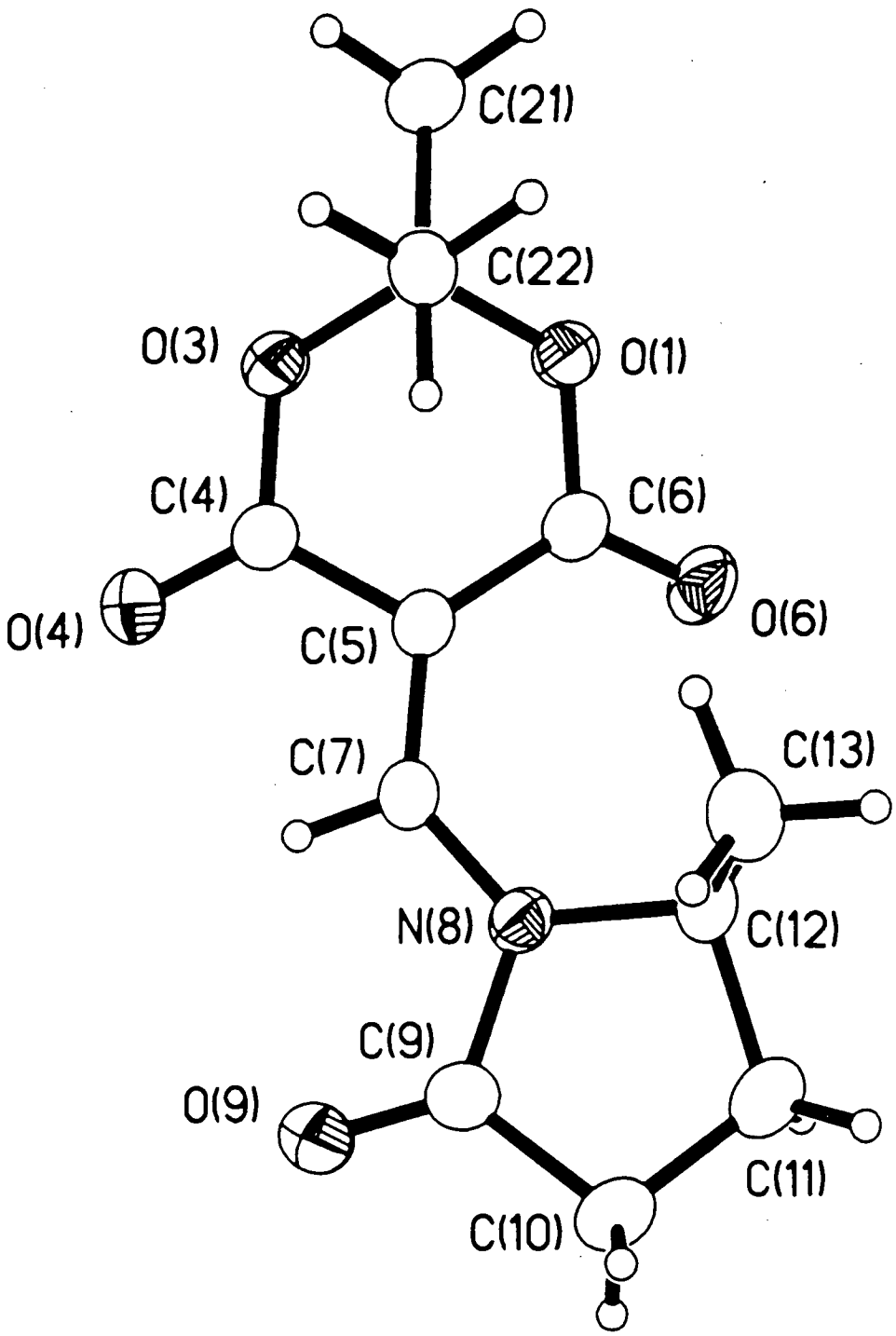
Table 21

Compound	Chemical Shift (p.p.m.)							
199	CH_3 (2A) & (2B)	H(7)	C(2)	C(2A) & (2B)	C(4)/C(6)	C(5)	C(4)/C(6)	C(7)
a	1.71	8.69	103.93	26.88	163.67	94.73	159.23	147.20
b	1.68 & 1.70	8.62	103.77	27.20 & 26.41	163.77	94.65	159.17	145.89
c	1.70	9.00	103.80	26.86	163.59	96.28	159.07	152.59
d*	1.66	8.47	103.62	26.48	164.45	89.87	159.49	148.78
e	1.75	9.24	103.89	27.09	163.25 or 163.60	95.88	159.39	153.41
f	1.75	9.04	104.04	27.03	163.80	94.51	159.82	146.95

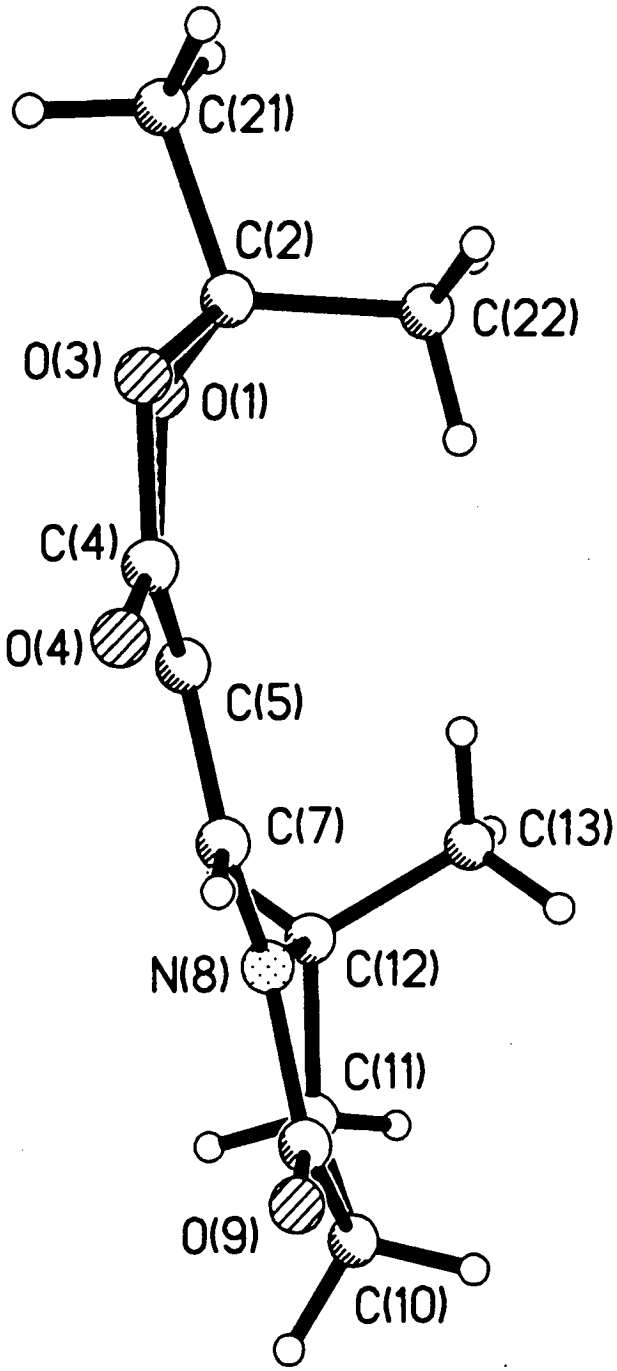
* [$^{2}H_6$]DMSO

The figures in **Table 21** show great consistency over the range of amide substituents. In compound **199b** the methyl group signals on the Meldrum's acid ring appeared as two separate singlets in the ^{1}H and ^{13}C spectra, and this can be explained by examining the crystal structure of the compound, as shown in **Schemes 47** and **48**.

Scheme 48 shows a side view of the molecule; the methyl group on the pyrrolidinone ring [C(13)] is out of plane with respect to the plane of the Meldrum's acid ring and consequently the two Meldrum's acid methyl groups are in two different environments, giving rise to separate signals in the NMR.



Scheme 47



Scheme 48

Table 22 - Bond Lengths (Å)

O(1)-C(6)	1.358(2)
O(1)-C(2)	1.440(2)
C(2)-O(3)	1.438(2)
C(2)-C(21)	1.502(2)
C(2)-C(22)	1.505(2)
O(3)-C(4)	1.361(2)
C(4)-O(4)	1.203(2)
C(4)-C(5)	1.477(2)
C(5)-C(7)	1.364(2)
C(5)-C(6)	1.467(2)
C(6)-O(6)	1.210(2)
C(7)-N(8)	1.351(2)
N(8)-C(9)	1.422(3)
O(9)-C(9)	1.205(2)
C(9)-C(10)	1.494(2)
N(8)-C(12)	1.468(2)
C(10)-C(11)	1.510(3)
C(11)-C(12)	1.533(2)
C(12)-C(13)	1.513(3)

Table 23 - Bond Angles (degrees)

C(6)-O(1)-C(2)	119.40(12)
O(1)-C(2)-O(3)	109.28(13)
O(3)-C(2)-C(21)	106.03(13)
O(1)-C(2)-C(21)	105.69(13)
O(3)-C(2)-C(22)	110.68(13)
O(1)-C(2)-C(22)	110.87(13)
C(21)-C(2)-C(22)	114.0(2)
C(4)-O(3)-C(2)	117.98(12)
O(4)-C(4)-O(3)	118.32(14)
O(4)-C(4)-C(5)	125.8(2)
O(3)-C(4)-C(5)	115.82(14)
C(7)-C(5)-C(6)	127.6(2)
C(7)-C(5)-C(4)	114.45(14)
C(4)-C(5)-C(6)	117.68(14)
O(6)-C(6)-O(1)	117.4(2)
O(6)-C(6)-C(5)	126.4(2)
O(1)-C(6)-C(5)	116.05(14)
N(8)-C(7)-C(5)	133.5(2)
C(7)-N(8)-C(9)	118.46(13)
C(7)-N(8)-C(12)	129.28(14)
C(9)-N(8)-C(12)	111.48(13)
O(9)-C(9)-N(8)	123.4(2)
O(9)-C(9)-C(10)	128.6(2)
N(8)-C(9)-C(10)	107.97(14)
C(9)-C(10)-C(11)	105.67(14)
C(10)-O(11)-C(12)	106.21(14)
N(8)-C(12)-C(13)	109.63(13)
N(8)-C(12)-C(11)	102.46(13)
C(13)-C(12)-C(11)	114.6(2)

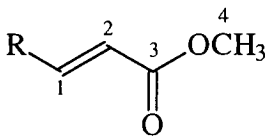
Table 24 - Torsion Angles (degrees)

C(6)-O(1)-C(2)-C(3)	-46.9(2)
C(6)-O(1)-C(2)-C(21)	-160.62(14)
C(6)-O(1)-C(2)-C(22)	75.4(2)
O(1)-C(2)-O(3)-C(4)	52.2(2)
C(21)-C(2)-O(3)-C(4)	165.66(13)
C(22)-C(2)-O(3)-C(4)	-70.2(2)
C(2)-O(3)-C(4)-O(4)	161.87(14)
C(2)-O(3)-C(4)-C(5)	-21.3(2)
O(4)-C(4)-C(5)-C(7)	-15.0(2)
O(3)-C(4)-C(5)-C(7)	168.35(14)
O(4)-C(4)-C(5)-C(6)	159.8(2)
O(3)-C(4)-C(5)-C(6)	-16.8(2)
C(12)-N(8)-C(9)-C(10)	-6.9(2)
N(8)-C(9)-C(10)-C(11)	-9.4(2)
C(7)-N(8)-C(12)-C(13)	67.4(2)
C(7)-N(8)-C(12)-C(11)	-170.5(2)
C(10)-C(11)-C(12)-N(8)	-24.8(2)
C(5)-C(7)-N(8)-C(12)	10.0(3)
C(2)-O(1)-C(6)-O(6)	-172.8(2)
C(2)-O(1)-C(6)-C(5)	-11.3(2)
C(7)-C(5)-C(6)-O(6)	20.5(3)
C(4)-C(5)-C(6)-O(6)	-153.6(2)
C(7)-C(5)-C(6)-O(1)	-164.1(2)
C(4)-C(5)-C(6)-O(1)	21.9(2)
C(4)-C(5)-C(7)-N(8)	-175.6(2)
C(6)-C(5)-C(7)-N(8)	10.2(3)
C(5)-C(7)-N(8)-C(9)	179.0(2)
C(7)-N(8)-C(9)-O(9)	1.9(2)
C(7)-N(8)-C(9)-C(10)	-177.79(14)
C(12)-N(8)-C(9)-O(9)	172.7(2)
O(9)-C(9)-C(10)-C(11)	170.9(2)
C(9)-C(10)-C(11)-C(12)	21.5(2)
C(9)-N(8)-C(12)-C(13)	-102.2(2)
C(9)-N(8)-C(12)-C(11)	19.9(2)
C(10)-C(11)-C(12)-C(13)	93.8(2)

The crystal structure of the compound shown in **Scheme 47** is extremely similar to that reported earlier for the 5-(*N*-acetamidomethylidene) Meldrum's acid derivative **153a**. The lone pair of N(8) can be delocalised into the carbonyl group of the pyrrolidinone ring, so shortening the N(8)-C(9) bond [1.422(2) Å] compared with the other four bonds in the ring [average 1.506(2) Å]. The lone pair can also be delocalised into the Meldrum's acid ring carbonyl groups, C(4)-O(4) and C(6)-O(6), and this is reflected in the N(8)-C(7) single bond [1.351(2) Å], which shows significant double bond character, and the C(5)-C(7) double bond [1.364(2) Å] which shows significant single bond character. The *N*-acetamido compound has N(8)-C(7) and C(5)-C(7) bond lengths of 1.351(6) Å and 1.360(7) Å respectively.

The compound is unable to form a six-membered hydrogen bonded ring, as in the *N*-acetamido derivative, but seven-membered, non-bonded contacts utilising H(12) and O(6) force the C(6)-C(5)-C(7) and C(5)-C(7)-N(8) bond angles to be much larger than in the *N*-acetamido derivative, 127.6(2)° and 133.5(2)° compared with 123.2(4)° and 127.6(5)° respectively. In the molecule, H(12) is forced close to the carbonyl group in the Meldrum's acid ring as all the carbonyl groups (and methyl substituent) try to stay as far apart as possible to minimise steric interactions.

A number of the reactions between the secondary cyclic amides were allowed to continue for longer periods of time, and were monitored by ^{1}H NMR spectroscopy. As observed previously, the signals due to the Meldrum's acid ring CH_3 groups and the methine proton disappeared, and two sets of doublets appeared at approximately 5 p.p.m. and 8 p.p.m., indicating the formation of prop-2-enoate compounds. Compounds **200b-e** were produced by this method, in yields ranging from 19-58%.



200

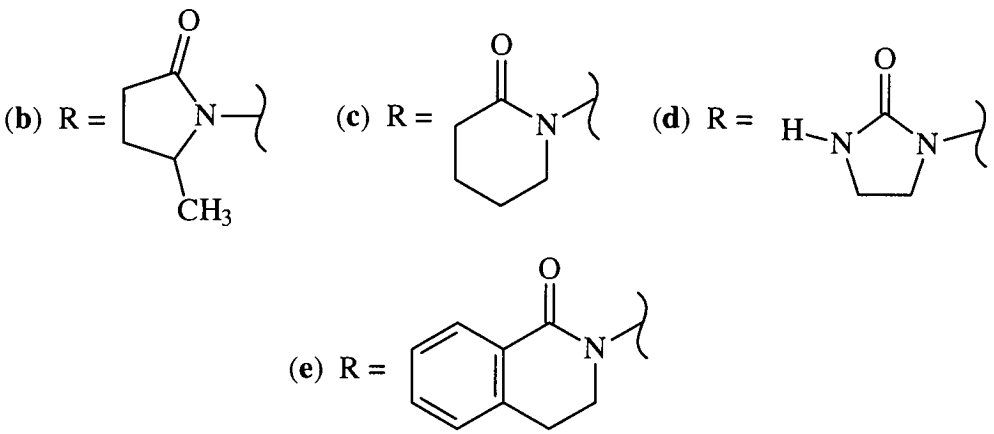


Table 25 contains a selection of ^{1}H and ^{13}C chemical shifts for this group of compounds, and includes those from the prop-2-enoates produced from secondary acyclic amides (**174a-c**) for comparison. All spectra were recorded in [^{2}H] chloroform unless otherwise indicated.

Table 25

	Chemical Shift (p.p.m.)							^{3}J (Hz)
Compound	C(1)	C(2)	C(3)	C(4)	OCH_3	H(1)	H(2)	H(1)/H(2)
200a	137.14	99.85	167.34	51.08	3.65	8.01	5.13	14.3
200b	136.18	99.85	167.51	51.09	3.66	7.93	5.21	14.5
200c	140.68	99.18	167.64	52.12	3.67	8.55	5.21	14.5
200d	138.86	95.45	167.85	51.04	3.68	8.01	4.94	14.3
200e	140.82	99.35	167.71	51.16	3.70	8.66	5.36	14.5
174a	143.52	99.22	166.98	51.29	3.68	7.76	5.36	13.5
174b	143.21	95.17	168.52	51.10	3.68	8.21	5.06	13.7
174c	146.36	94.13	168.29	51.04	3.65	7.72	4.99	13.6

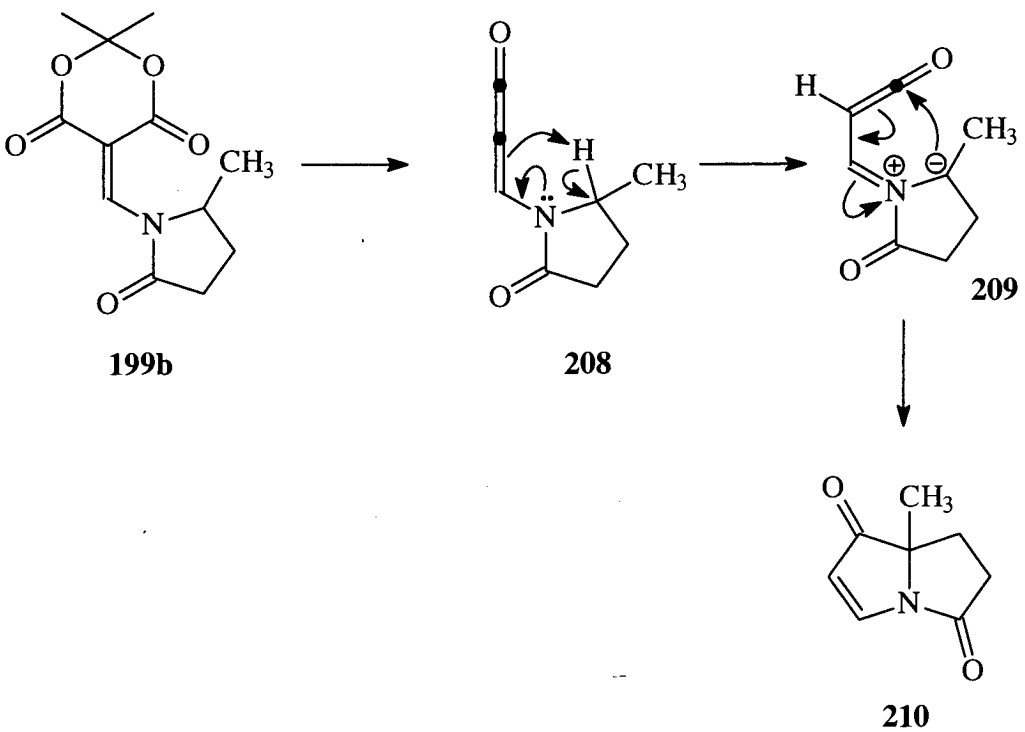
Across the range of R substituents, the figures in **Table 25** show a great deal of consistency. C(1) and H(1) are electron poor atoms and C(2) and H(2) electron rich atoms due to the delocalisation of the nitrogen atom lone pair in the substituent through the propenoate chain.

Looking particularly at the C(2) chemical shifts, three entries in this column, for compounds **200d**, **174b**, and **174c** are at significantly lower frequencies than the other five. These three compounds are derived from ureas, and the presence of a second nitrogen atom in the compounds has a significant effect on the C(2) chemical shift. This second nitrogen atom can also delocalise its lone pair into the carbonyl group in the substituent, leaving the other nitrogen atom attached directly to the propenoate chain able to delocalise a greater proportion of its lone pair into this chain, so producing a more electron rich site at C(2). This is also reflected in the chemical shift of H(2) in these three compounds, with 4.94 p.p.m., 4.99 p.p.m. and 5.06 p.p.m. being the three lowest frequency figures in this column. The chemical shifts associated with the ester group are effectively unchanged by an alteration in the R substituent.

(b) Pyrolyses of Cyclic 5-(*N*-Amidomethylidene) Meldrum's Acid Derivatives and Related Compounds

(i) Pyrolyses of derivatives produced from cyclic 5-membered ring amides

Pyrolysis of the derivative produced from 5-methylpyrrolidin-2-one **199b** at a standard furnace temperature of 600 °C gave a mixture of products, which contained unreacted starting material, indicating a higher furnace temperature was needed. Increasing the furnace temperature to 700 °C gave no starting material in the pyrolysate and further examination by ^{1}H NMR spectroscopy showed that the bicyclic product **210** had been produced, as illustrated in **Scheme 49**.



Scheme 49

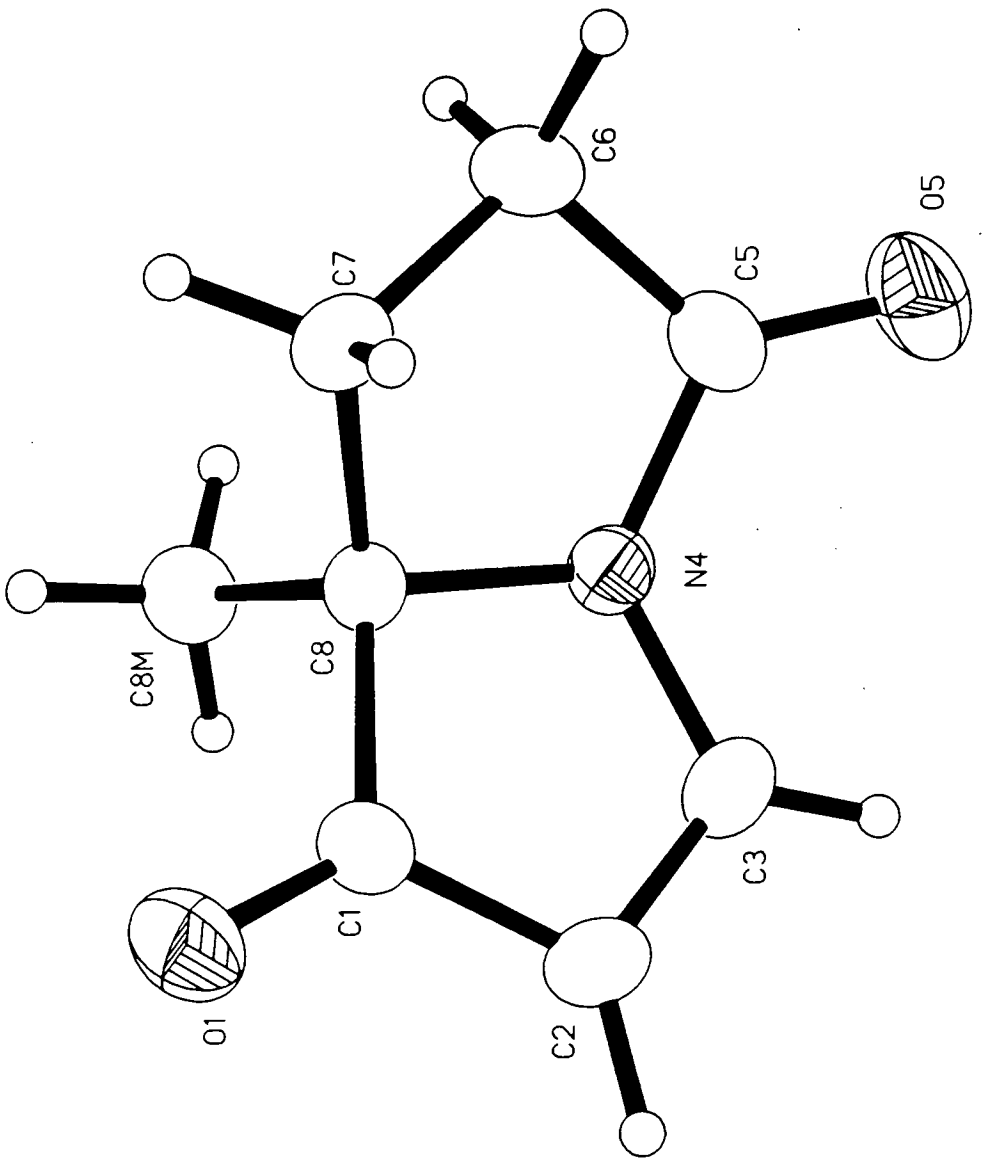
Collapse of the Meldrum's acid ring in **199b** with loss of acetone and carbon dioxide produced the methylideneketene **208**. This underwent a hydrogen shift to produce the intermediate **209**. This intermediate carries a formal positive charge on a nitrogen

atom connected to an electron-withdrawing group and this would be expected to be a very unfavourable situation. However the pyrolysis successfully produced 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione **210** in a yield of 68% by cyclisation of intermediate **209**. The higher than normal furnace temperature required (700 °C) can be explained by the necessary formation of this unfavourable intermediate in order to produce the pyrrolizinedione system.

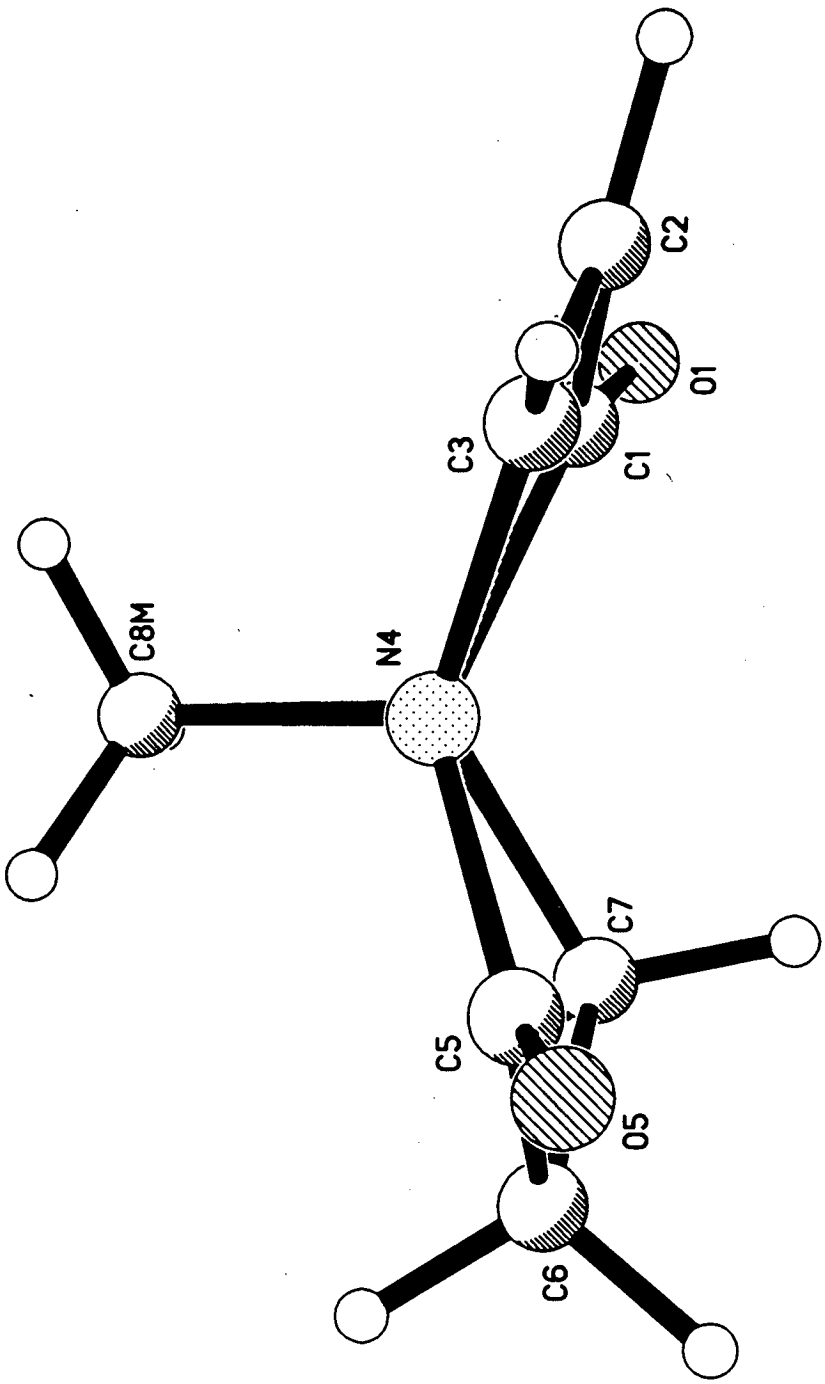
The bicyclic product proved particularly difficult to recrystallise; however sublimation produced the compound in a highly crystalline form, with crystals of X-ray crystallographic quality. Consequently, an X-ray structure of the pyrrolizinedione was obtained and is shown in **Schemes 50** and **51** with associated bond lengths, bond angles and torsion angles in **Tables 26, 27** and **28** respectively.

The side view of the molecule in **Scheme 51** shows its geometry to be "butterfly-shaped", with the methyl group C(8M) pointing directly away from the two rings. Unlike *N*-alkyl and *N*-aryl pyrrolones[140,141] the stereochemistry at the nitrogen atom is not planar, with an angle between best planes of 143.5°.

The nitrogen atom lone pair can be delocalised in two directions, into the amide carbonyl group C(5)-O(5) in the "right-hand" ring and into the pyrrolone-type carbonyl group C(1)-O(1) in the "left-hand" ring. This is reflected in the N(4)-C(5) and N(4)-C(3) bond lengths [1.389(2) Å and 1.385(2) Å respectively] which both show some double bond character, and the C(2)-C(3) bond length [1.336(3) Å] which shows some single bond character.



Scheme 50



Scheme 51

Table 26 - Bond Lengths (Å)

C(1)-O(1)	1.218(2)
C(1)-C(2)	1.447(2)
C(1)-C(8)	1.531(2)
C(2)-C(3)	1.336(3)
C(3)-N(4)	1.385(2)
N(4)-C(5)	1.389(2)
N(4)-C(8)	1.469(2)
C(5)-O(5)	1.208(2)
C(5)-C(6)	1.500(3)
C(6)-C(7)	1.527(2)
C(7)-C(8)	1.529(2)
C(8)-C(8M)	1.530(2)

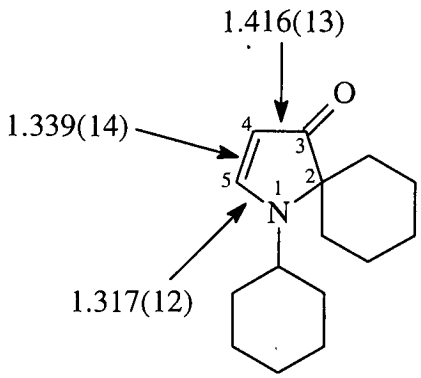
Table 27 - Bond Angles (degrees)

O(1)-C(1)-C(2)	125.8(2)
O(1)-C(1)-C(8)	124.7(2)
C(2)-C(1)-C(8)	106.81(14)
C(3)-C(2)-C(1)	108.5(2)
C(2)-C(3)-N(4)	112.4(2)
C(3)-N(4)-C(5)	126.14(14)
C(3)-N(4)-C(8)	109.58(13)
C(5)-N(4)-C(8)	112.87(14)
O(5)-C(5)-N(4)	124.5(2)
O(5)-C(5)-C(6)	129.0(2)
N(4)-C(5)-C(6)	106.47(14)
C(5)-C(6)-C(7)	104.40(14)
C(6)-C(7)-C(8)	102.91(13)
N(4)-C(8)-C(7)	103.13(12)
N(4)-C(8)-C(8M)	111.03(13)
C(7)-C(8)-C(8M)	112.25(14)
N(4)-C(8)-C(1)	101.72(12)
C(7)-C(8)-C(1)	118.93(13)
C(8M)-C(8)-C(1)	108.99(13)

Table 28 - Torsion Angles (degrees)

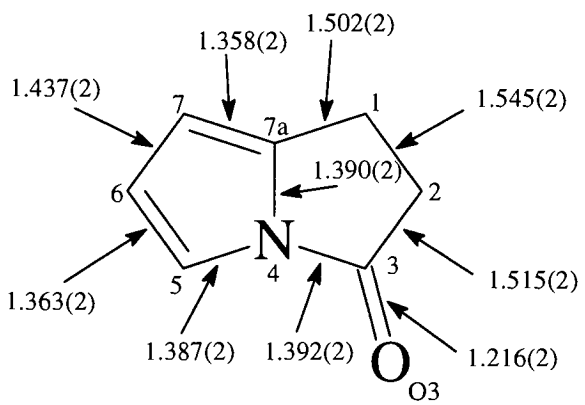
O(1)-C(1)-C(2)-C(3)	-172.2(2)
C(8)-C(1)-C(2)-C(3)	9.1(2)
C(1)-C(2)-C(3)-N(4)	-4.5(2)
C(2)-C(3)-N(4)-C(5)	138.1(2)
C(2)-C(3)-N(4)-C(8)	-2.3(2)
C(3)-N(4)-C(5)-O(5)	34.7(3)
C(8)-N(4)-C(5)-O(5)	174.0(2)
C(3)-N(4)-C(5)-C(6)	-144.7(2)
C(8)-N(4)-C(5)-C(6)	-5.4(2)
O(5)-C(5)-C(6)-C(7)	-155.9(2)
N(4)-C(5)-C(6)-C(7)	23.4(2)
C(5)-C(6)-C(7)-C(8)	-31.7(2)
C(3)-N(4)-C(8)-C(7)	131.22(14)
C(5)-N(4)-C(8)-C(7)	-14.8(2)
C(3)-N(4)-C(8)-C(8M)	-108.4(2)
C(5)-N(4)-C(8)-C(8M)	105.6(2)
C(3)-N(4)-C(8)-C(1)	7.5(2)
C(5)-N(4)-C(8)-C(1)	-138.57(14)
C(6)-C(7)-C(8)-N(4)	28.0(2)
C(6)-C(7)-C(8)-C(8M)	-91.5(2)
C(6)-C(7)-C(8)-C(1)	139.6(2)
O(1)-C(1)-C(8)-N(4)	171.5(2)
C(2)-C(1)-C(8)-N(4)	-9.8(2)
O(1)-C(1)-C(8)-C(7)	59.1(2)
C(2)-C(1)-C(8)-C(7)	-122.1(2)
O(1)-C(1)-C(8)-C(8M)	-71.(2)
C(2)-C(1)-C(8)-C(8M)	107.5(2)

When compared to a pyrrolone, such as the compound illustrated in **Scheme 52**, which is very similar to the "left-hand" ring in the pyrrolizinedione **210**, the effect of the delocalisation of the nitrogen atom lone pair in two directions can be seen.



Scheme 52

In the pyrrolone in **Scheme 52**, the nitrogen atom lone pair is delocalised exclusively through the ring into the carbonyl group on C(3). This is reflected in, for example, the N(1)-C(5) bond which is much shorter than the corresponding C(3)-N(4) bond in the pyrrolizinedione [1.317(12) Å compared with 1.385(2) Å]. An X-ray structure of a similar compound,[142] 1,2-dihydropyrrolizine-3-one has been determined; bond lengths (in Angstroms) are illustrated in **Scheme 53**.

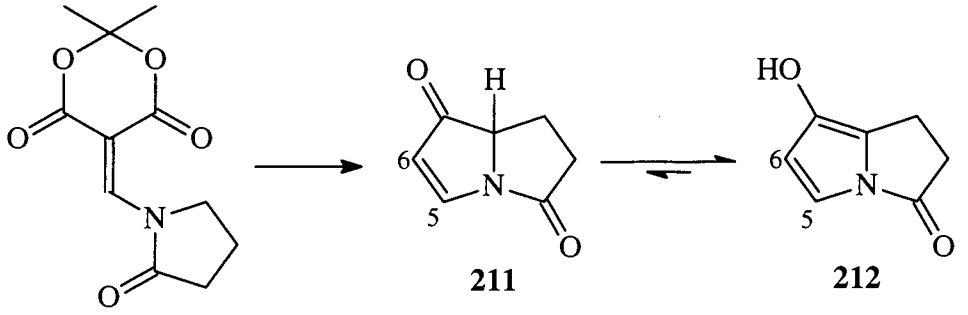


Scheme 53

The compound shows many similar characteristics to the pyrrolizinedione **210**, with its "push-pull" type system. The nitrogen atom's lone pair can delocalise into either

the amide-type carbonyl group or the pyrrole ring, producing the same lengthening and shortening of double and single bonds; in this case due to the conjugation, bonds C(7)-C(7a) and C(7a)-N(4) are also affected. The "right-hand" ring also shows very similar bond lengths to the pyrrolizinedione system.

Following the successful pyrolysis of the Meldrum's acid derivative produced from 5-methylpyrrolidin-2-one at 700 °C, compound **199a** was pyrolysed at the same temperature.

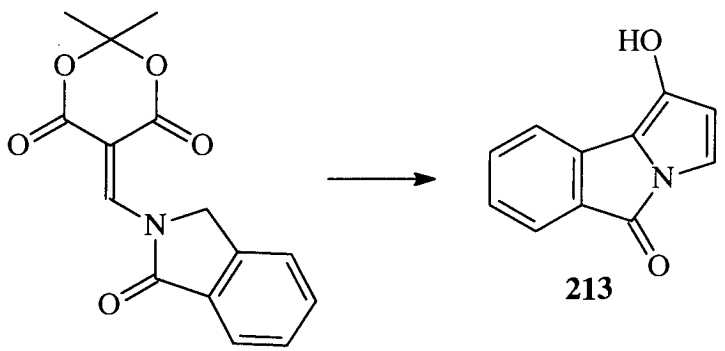


199a **211** **212**

The product (obtained in a yield of 62%) proved to be extremely insoluble in [^{2}H]chloroform; examination by ^{1}H NMR spectroscopy in [$^2H_6$]DMSO showed the product to be exclusively compound **212**, the enol tautomer, as would be expected in a hydrogen bond acceptor solvent. Changing the solvent to [$^2H_4$]methanol, a hydrogen bond donor solvent, would be expected to shift the equilibrium towards the keto form **211**, and this has been observed in 1*H*-pyrrol-3(2*H*)-ones;[141] indeed the ^{1}H NMR spectrum showed approximately 20% of the keto form **211** in this solvent. The two tautomers, keto and enol, were easily identifiable in the ^{1}H NMR spectrum. The pair of doublets associated with H(5) and H(6) have different chemical shifts depending on the tautomeric form of the compound; in the keto form the doublets have a much greater separation, appearing at approximately 8.1 p.p.m. and 5.6 p.p.m., whereas in the enol form the doublets are much closer together at approximately 6.8

p.p.m. and 6.0 p.p.m. The coupling constant of the H(4)/H(5) doublets is also slightly smaller in the enol tautomer, 3.1 Hz compared to 4.0 Hz in the keto tautomer.

The benzo analogue of this compound was also successfully prepared; pyrolysis (at 700 °C) of compound **199f** produced from the isoindolone gave the pyrroloisoindolone **213**. The pyrolysis was exceptionally clean, and the solid product could be scraped from the trap in a yield in excess of 80%.



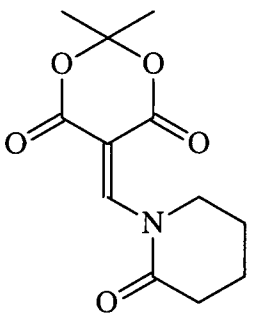
199f **213**

In [$^2H_6$]acetone, the product existed exclusively as the enol tautomer **213**, with the characteristic hydroxypyrrole doublets at 6.95 p.p.m. and 5.95 p.p.m. in the ^1H NMR spectrum, with a coupling constant of 3.4 Hz. Previous work with pyrrolones[141] showed [$^2H_6$]acetone favoured the hydroxypyrrole form, but with ~25% of the compound still existing in the pyrrolone form. Therefore it appears that these amide systems relatively favour the hydroxy tautomer by comparison with related *N*-arylpyrrolones.

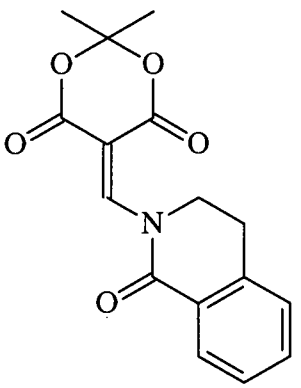
The three compounds prepared from five-membered ring amides all pyrolysed very cleanly and were produced in good yields, ranging from 62-80% after recrystallisation or sublimation. This result was somewhat surprising, considering the very unfavourable FVP intermediates required to produce these compounds, but the success of this route opens the door into a completely new area of chemistry, some of which is explored later in this chapter (see pages 166 and 194).

(ii) Pyrolyses of derivatives produced from cyclic 6-membered ring amides

Following the success of the pyrolyses of derivatives produced from cyclic 5-membered ring amides, this methodology was extended to derivatives **199c** and **199e**, produced from piperidin-2-one and 3,4-dihydroisoquinolin-1(2*H*)-one respectively, both 6-membered ring amides.



199c

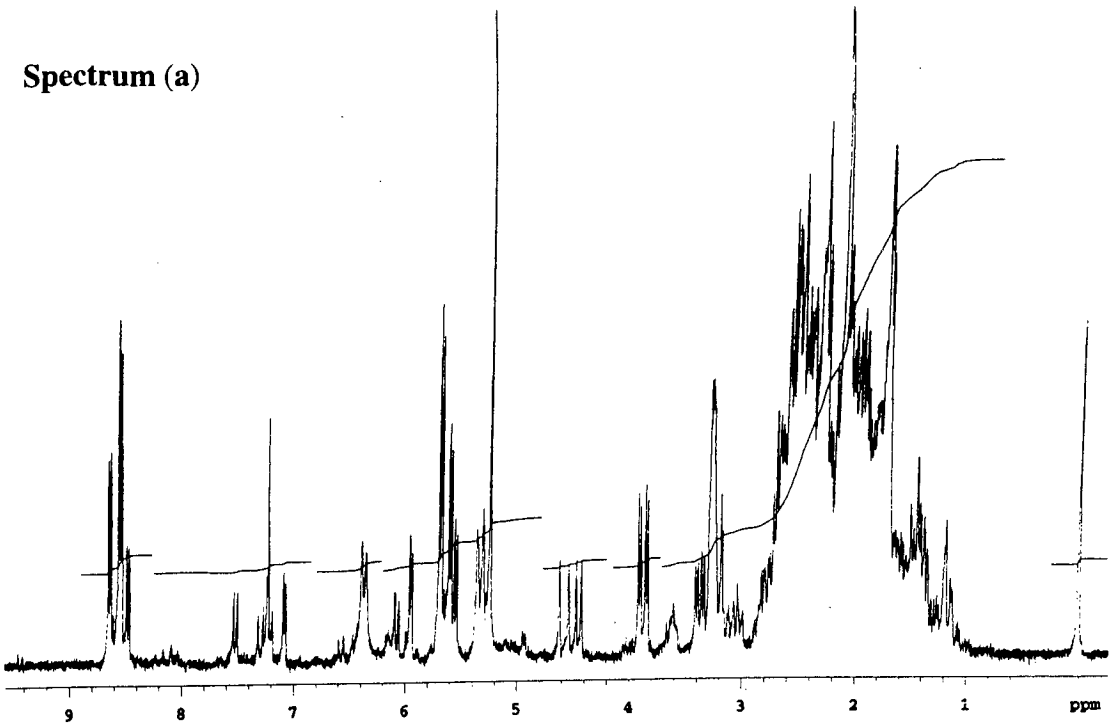


199e

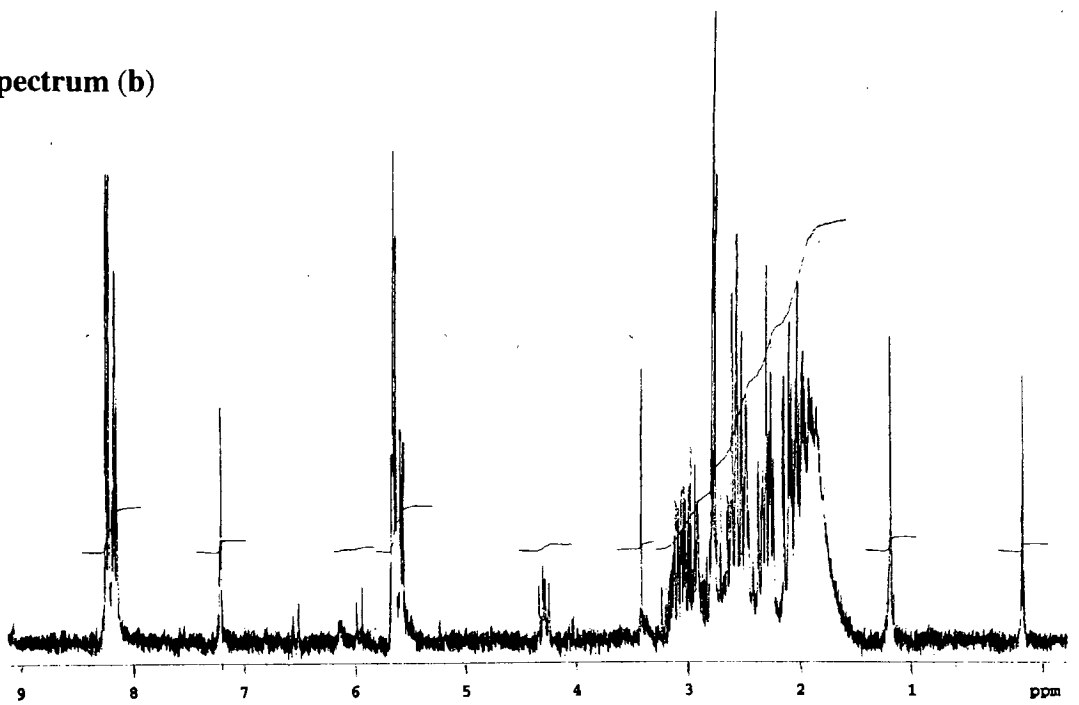
Pyrolysis of derivatives **199c** at 700 °C, the optimum temperature for the three previous pyrolyses, and examination of the crude pyrolysate by ^{1}H NMR spectroscopy, showed quite a complex mixture, as shown in **Scheme 54**, **spectrum** (**a**).

This spectrum, recorded in [^{2}H]chloroform, shows a high proportion of the integral over the alkyl region. A ^{1}H NMR spectrum of the crude pyrolysate of a derivative produced from a 5-membered ring amide, for example **spectrum** (**b**) in **Scheme 54** ([^{2}H]chloroform) from the pyrolysis of compound **199a** (prepared from the pyrrolidin-2-one), also showed this, although to a slightly lesser extent. However, when comparing peaks in the two spectra in the region 5-9 p.p.m., **spectrum** (**a**) shows much more complexity.

Spectrum (a)

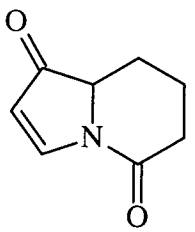


Spectrum (b)

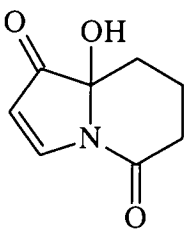


Scheme 54

Pyrolysis at higher and lower furnace temperatures (750 °C and 650 °C) had little effect on the content of the pyrolysate, and at this stage it was not possible to make any definite assignments, although it was possible some of the peaks were due to the desired product **214**.



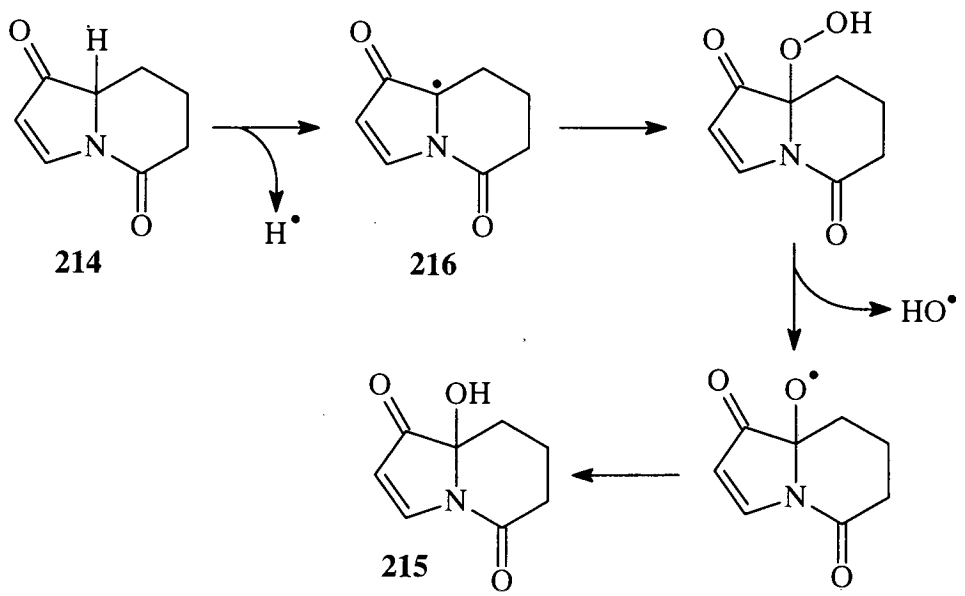
214



215

The pyrolysis was scaled up (at 700 °C) and the pyrolysate subjected to dry flash column chromatography. However, the only identifiable product obtained was shown by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry to be compound **215**, the autoxidised product. This was obtained in a very low yield of 14%; recovery was less than expected on the basis of the crude ^{1}H NMR spectrum.

The autoxidation at the ring junction can occur *via* the route shown in **Scheme 55**.

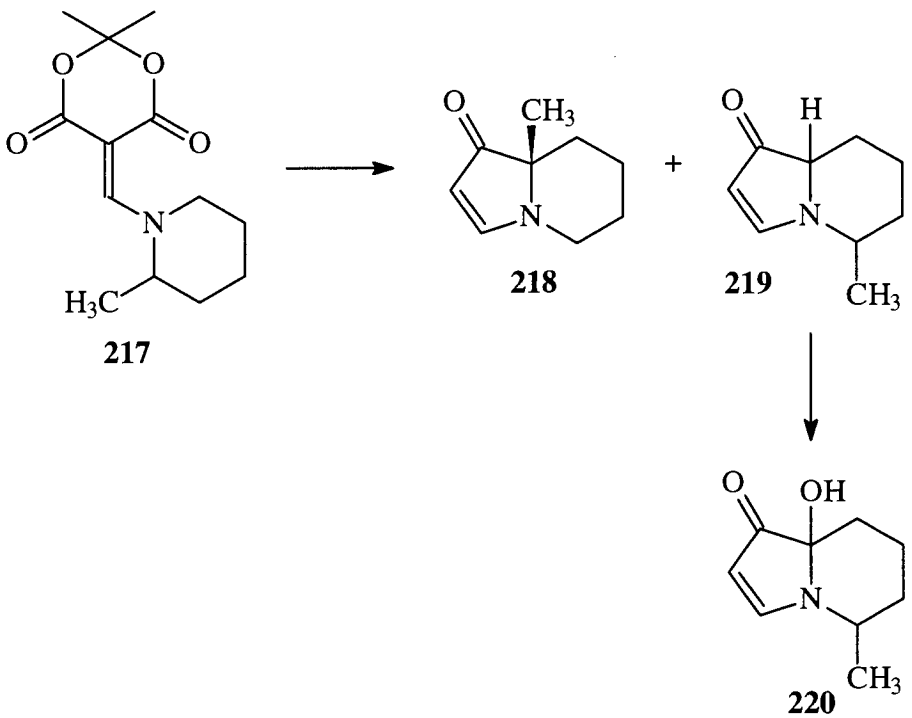


Scheme 55

Compound **214**, the expected pyrolysis product can form radical **216**; this radical has the advantage of being captodative[116] (see page 71 for a detailed explanation of this effect), and so has extra stabilisation. The radical can go on to react with atmospheric oxygen, ultimately to produce the hydroxy compound **215**, as illustrated, with the hydroxyl radical produced able to perpetuate the autoxidation reaction.

Due to the complex nature of the ^1H NMR spectrum of the crude pyrolysate it was not possible to tell if autoxidation had occurred immediately upon pyrolysis of the Meldrum's acid derivative, or during column chromatography, but this work with the 6-membered ring amide derivative shows it to be much more susceptible to autoxidation than the corresponding work with a comparable 5-membered ring amide derivative.

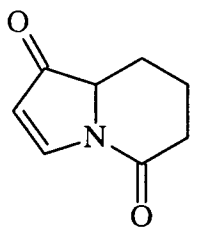
Previous work in this area[143] was concerned with a similar Meldrum's acid derivative **217**, produced from 6-methylpiperidine.



217 **218** **219** **220**

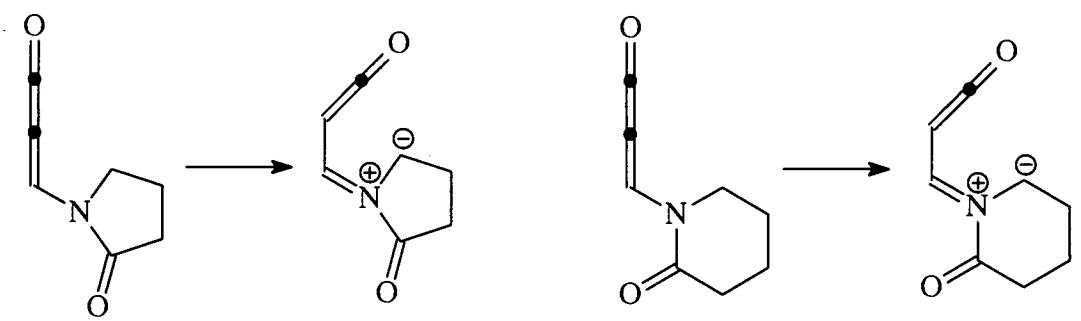
Pyrolysis of derivative **217** at 600 °C produced a mixture of two isomeric tetrahydroindolizinones **218** and **219** which were inseparable. However, on exposure to air, compound **219** spontaneously autoxidised to give the hydroxy compound **220** and this compound could be separated from compound **218**. Both compounds **218** and **220** were produced in very low yields of only 20% and 16% respectively.

The lack of the desired pyrolysis product **214** from the pyrolysis of the Meldrum's acid derivative appears to be due to a combination of two factors.



214

Firstly, the pyrolysis of the derivative itself is much poorer than those from derivatives produced from cyclic 5-membered ring amides. **Scheme 56** illustrates the pyrolysis intermediates that would be formed from the 5- and 6-membered ring amide derivatives.

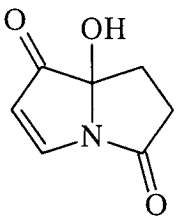


221 **222** **223** **224**

Scheme 56

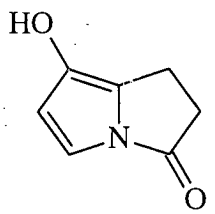
In both cases, conversion of the methylideneketenes (**221** and **223**) to the dipolar intermediates (**222** and **224**) requires the formation of a carbon atom with carbanion character in the amide ring. The carbanion-like carbon atom is sp^2 hybridised, resulting in angles at that carbon atom of 120°. This is more compatible with the shape of the 5-membered ring than the 6-membered ring; the most stable form of the latter is the chair formation and this would require a more significant shape distortion than in the 5-membered ring amide derivative to accommodate the carbanion-like carbon atom. Consequently the energy barrier for the conversion of **223** to **224** in the 6-membered ring amide derivative would be expected to be slightly higher than for the corresponding conversion of **221** to **222** in the 5-membered ring amide derivative, making the former step slightly less favourable.

The second factor is the instability of the pyrolysis product to aerial autoxidation. The pyrolysis products of both the derivative produced from piperidin-2-one and the derivative produced from 6-methylpiperidine reported previously[143] showed evidence of this. However the 5-membered ring amide derivative pyrolysed successfully to the 7-hydroxypyrrolizin-3-one, and the autoxidised pyrrolizinedione **225** which could theoretically be formed as the ring junction is unsubstituted, was never isolated, (although extremely minor peaks could be observed in the ^{1}H NMR spectrum which may have been due to the formation of compound **225**). This is perhaps reflected in the physical state of the pyrolysis products. The crude pyrolysates of the two derivatives produced from 5-membered ring amides could be scraped from the trap as crystalline solids (i.e. compounds **210** and **212**) whereas the crude pyrolysate of compound **199c** (produced from piperidin-2-one) was a sticky oil which did not solidify.



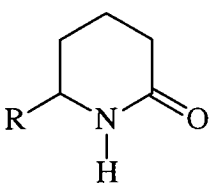
225

This information implies that the rate at which the product from the pyrolysis of 6-membered ring amide autoxidises is much faster than the rate of autoxidation of the product formed from the 5-membered ring amide. Autoxidation at the ring junction was observed however when compound **212** was subjected to hydrogenation (see page 195 later in this chapter) indicating this 5-5 bicyclic system is susceptible to this type of reaction under certain conditions.



212

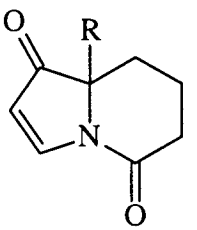
In an attempt to rationalise the poor pyrolysis results from the 6-membered ring amide derivative, two amides, **226a** and **226b**, substituted in the 6-position, were prepared.



(**a**) R = C_6H_5
(**b**) R = CH_3

226

These amides would ultimately be expected to give fused 5-6 membered ring systems **227a** and **227b** respectively after successful pyrolyses of the appropriate Meldrum's acid derivatives, with the ring junction position blocked by a substituent, so removing the possibility of autoxidation at this site. Consequently, any differences in the pyrolyses compared with those of the 5-membered ring amides could be attributed to the factors of ring size, and differences in the pyrolysis intermediates produced *en route* to the fused 5-6 membered ring system.

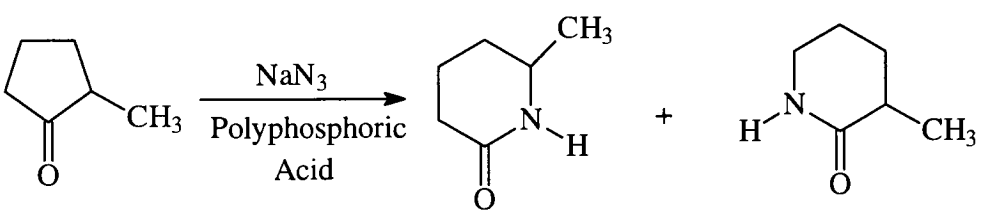


(**a**) R = C_6H_5
(**b**) R = CH_3

227

6-Phenylpiperidin-2-one **226a**, was prepared from 4-benzoylbutyric acid, formic acid and ammonium carbonate by the method of de Graff *et al*;[144] but only in a moderate yield of 41%. This was due to the need for repeated recrystallisations in order to obtain the cyclic amide in a pure enough form to use in the next step.

Attempts to prepare 6-methylpiperidin-2-one from 2-methylpentanone **229** using the method of Conley[145] unexpectedly produced a mixture of compounds. Spectroscopic work showed the mixture to be comprised of the desired compound **226b**, and the undesired compound **228** as shown in **Scheme 57**.

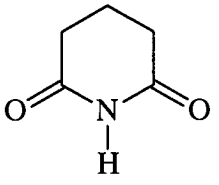


229 **226b** **228**

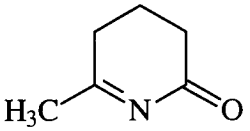
Scheme 57

The two products were formed in a ratio of 1.5:1, with the desired compound the major product, but the two proved to be inseparable by dry flash column chromatography. This result was in complete contrast to that of Conley, who reported the preparation of compound **226b** in a yield of 89% by this method, (confirming the product identity by melting point), with no evidence of a second product being formed.

Consequently another approach[146] was tried, and 6-methylpiperidin-2-one **226b**, was successfully prepared from glutarimide **230** *via* a Grignard reaction and subsequent reduction of the reaction intermediate **231**, but in only a moderate yield of 37%.



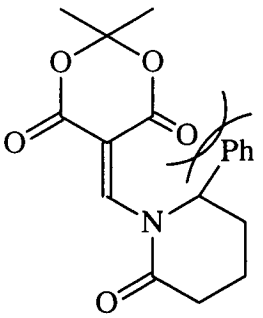
230



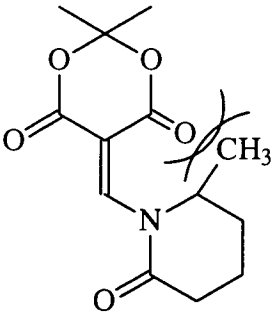
231

Both amides were reacted with 5-methoxymethylidene Meldrum's acid, using the standard conditions of refluxing acetonitrile. However, even with extended reflux times, both amides failed to react and unreacted starting material was recovered from the reactions. 5-Methoxymethylidene Meldrum's acid was also degraded under these conditions.

Examining the structure of the expected products **232** and **233** shows a possible reason why the reactions with the two amides failed to produce these derivatives.



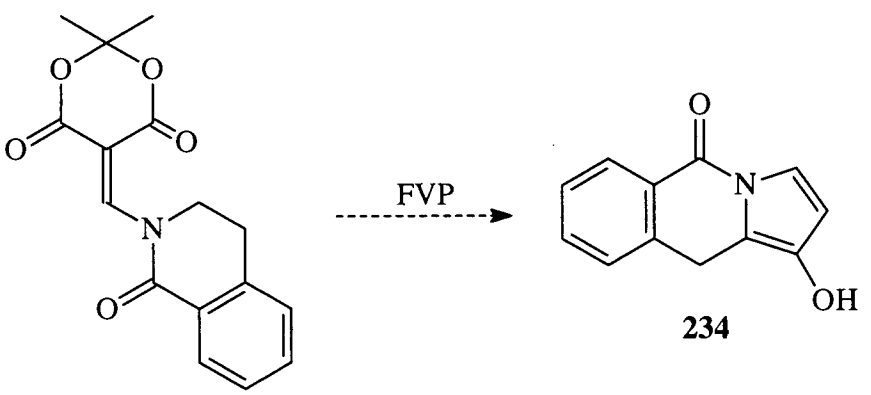
232



233

From the earlier X-ray of the Meldrum's acid derivative produced from 5-methylpyrrolidin-2-one, the configurations shown in **232** and **233** would be expected, with the amide ring carbonyl orientated away from the carbonyl group in the Meldrum's acid ring to minimise steric and repulsive interactions. The consequence of this is to force the amide ring substituent at the 6-position (methyl or phenyl) close to the carbonyl group in the Meldrum's acid ring, which itself generates an unacceptable level of steric hindrance. Hence, no reaction takes place between the amides and 5-methoxymethylidene Meldrum's acid under the conditions used and this line of investigation was not pursued further.

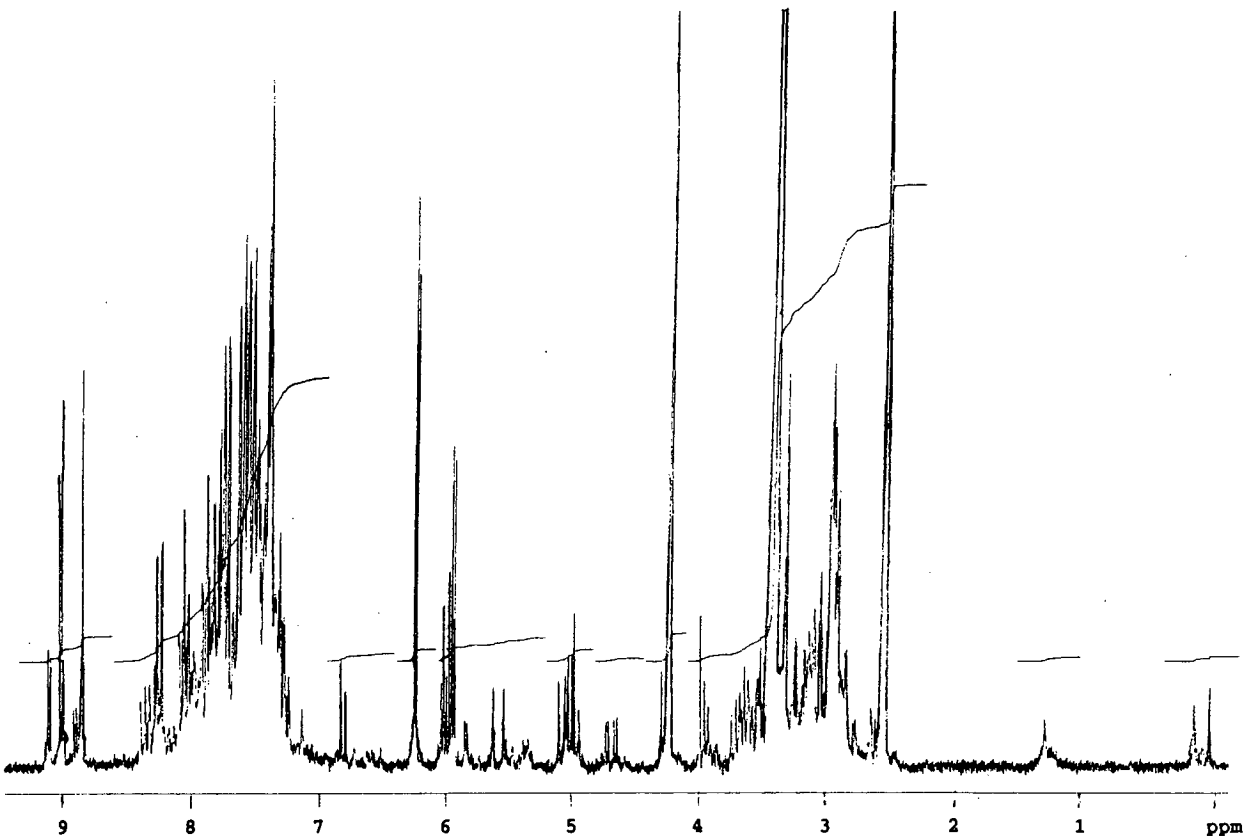
The second compound prepared, **199e** was pyrolysed at 700 °C, and was expected to give the fused 3-ring compound **234**.



199e

234

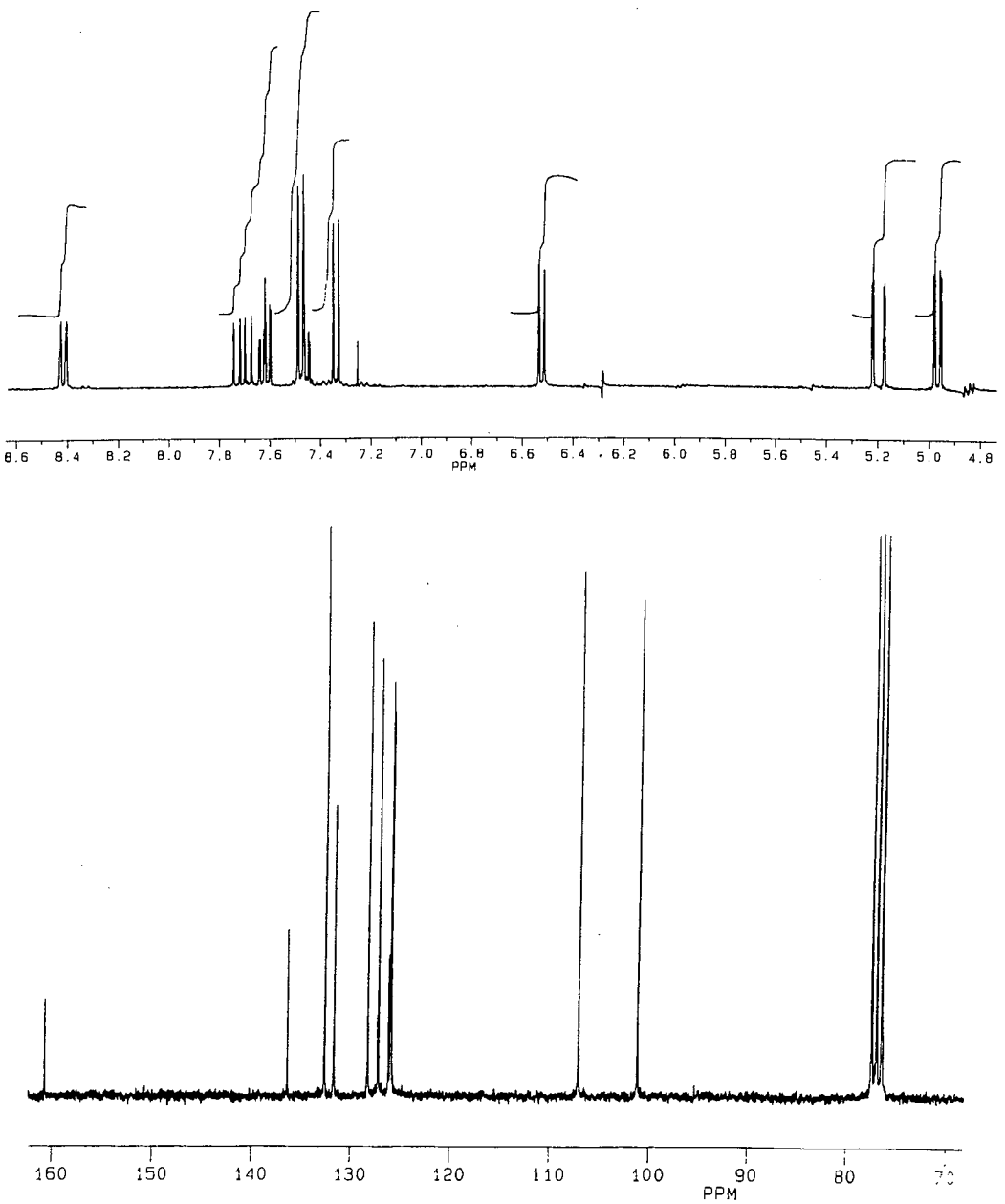
However, examination of the pyrolysate by ^1H NMR spectroscopy showed it to be a highly complex mixture, with a high proportion of the total integral over the aromatic region of the spectrum. Repeating the pyrolysis over a range of temperatures (500 - 800 °C) again gave highly complex mixtures of products; the temperature giving the least complex mixture (700 °C) was pyrolysed on a larger scale and the products were subjected to dry flash column chromatography. **Scheme 58** illustrates the ^1H NMR spectrum (in $[^2H_6]$DMSO) of the pyrolysate from a large scale pyrolysis of **199e**.



Scheme 58

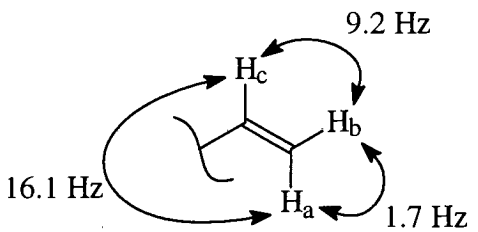
Only one product was isolated from the column and in a very small yield of only 2%. This is perhaps again due to the instability of products from a compound containing a 6-membered ring amide to autoxidation, and the problems associated with forming an sp^2 hybridised carbanion-like carbon atom in the amide ring during pyrolysis.

The compound obtained was examined by ^{1}H and ^{13}C NMR spectroscopy (at 360 MHz) and mass spectrometry in order to identify it. **Scheme 59** illustrates the ^{1}H and ^{13}C NMR spectra of the compound (in [^{2}H]chloroform). The ^{13}C spectrum indicated the compound contained 11 carbon atoms, comprised of 3 quaternary carbon atoms, 7 CH carbon atoms and 1 CH_2 carbon atom. The ^{1}H spectrum was examined in detail, and was subjected to various decoupling and n.O.e. experiments.



Scheme 59

The doublets of doublets at 4.97, 5.20 and 7.70 p.p.m. corresponded to an ethenyl group, with coupling constants of 1.7, 9.2 and 16.1 Hz (typical of this functional group), as shown in **Scheme 60**. Irradiation of H_c gave an n.O.e. enhancement of H_b of 3%.



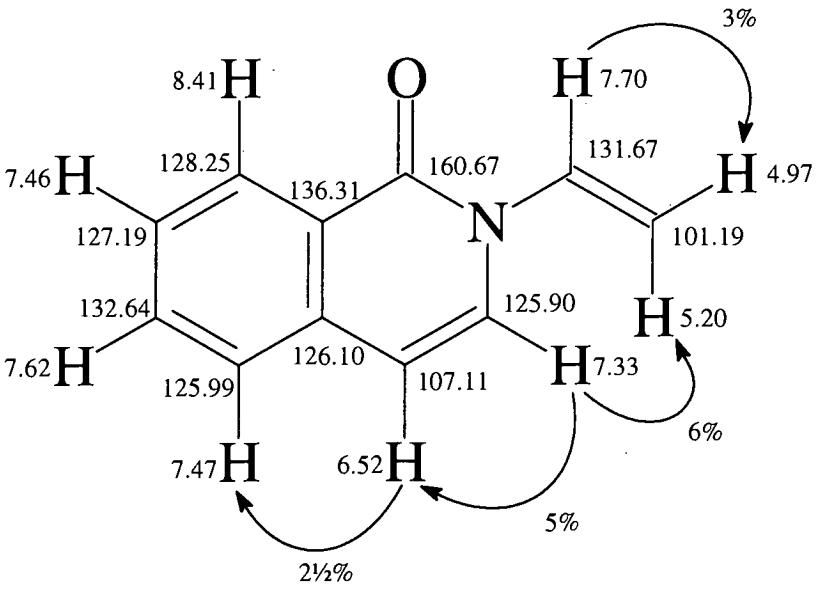
Scheme 60

The doublets at 6.52 and 7.33 p.p.m. have coupling constants of 7.6 Hz, and irradiation of the doublet at 6.52 p.p.m. reduced the doublet at 7.33 p.p.m. to a singlet. Further n.O.e. experiments showed that irradiation of the doublet at 7.33 p.p.m. enhanced the doublet at 6.52 p.p.m. by 5% as would be expected, but also H_a in the ethenyl group by 6%. This gave an indication of the proximity of the ethenyl group to the two protons giving rise to the two doublets, and also the orientation of the ethenyl group towards these protons. The chemical shift of the proton at 8.41 p.p.m. indicated its proximity to an electron-withdrawing carbonyl group and irradiation of this proton removed the fine coupling on multiplets in the aromatic region 7.62-7.46 p.p.m., indicating it was a proton on the benzene ring.

Mass spectrometry indicated a molecular ion of *m/z* 171, confirming the assumed formula of $C_{11}H_9NO$, and the breakdown pattern confirmed the existence of the ethenyl group with a peak at $M^+ - 27$.

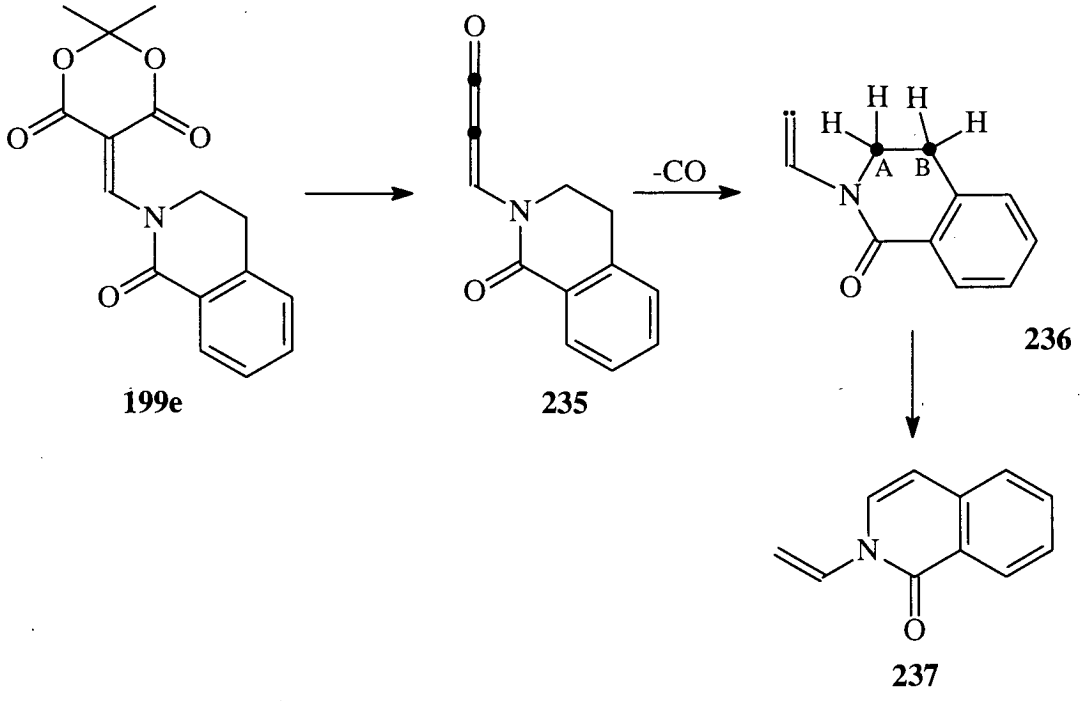
Combining all the information led to the assignment of the structure shown in **Scheme 61**, which also illustrates the complete NMR assignments (in p.p.m.) for the

proton and carbon atoms (which were confirmed by a C-H correlation experiment); all n.O.e. enhancements determined are also indicated.



Scheme 61

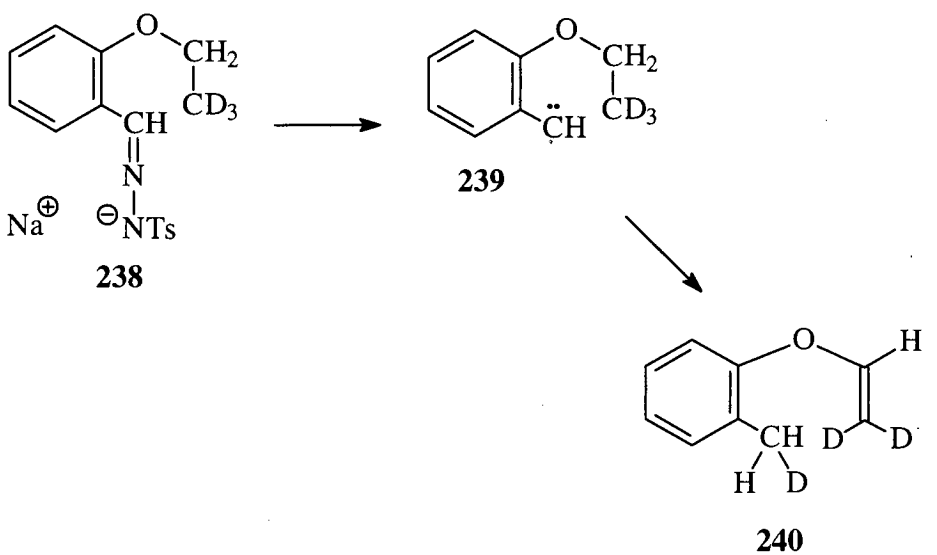
One possible mechanism for the production of this compound is shown in **Scheme 62**.



Scheme 62

Pyrolysis of the Meldrum's acid derivative **199e**, with the usual loss of carbon dioxide and acetone, produces the expected methylideneketene **235**. This intermediate could then lose carbon monoxide to give the carbene **236** which can abstract two protons, one from position A and one from position B on the amide ring, to give the *N*-ethenylisoquinolin-1(2*H*)-one **237**.

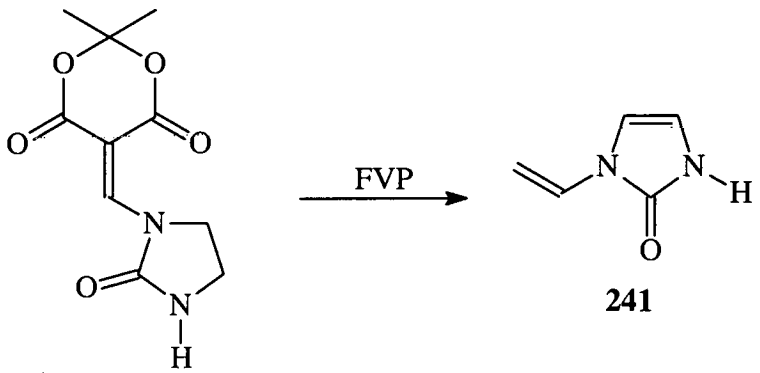
The abstraction of protons by a carbene function has some precedent in the literature. Work by Crow and McNab[147] on vicinal hydrogen abstraction using deuterium labelled compounds has illustrated this, and an example is shown in **Scheme 63**.



Scheme 63

Pyrolysis of the salt **238** generated the carbene **239**; this intermediate abstracted one proton from the CH_2 group and one deuterium atom from the CD_3 group to produce the vinyl ether **240** exclusively. The identity of the product was confirmed unambiguously by NMR spectroscopy, showing the distribution of deuterium was specific.

An identical type of reaction was observed when the Meldrum's acid derivative **199d**, prepared from a cyclic urea, was pyrolysed.



199d **241**

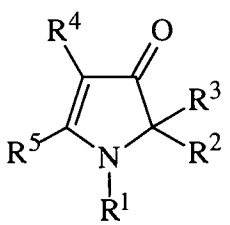
Compound **241**, the *N*-ethenylimidazolidinone was isolated from the pyrolysis, but in a yield of only 4%. Two factors contributed to very poor yield; firstly the starting material proved to be extremely involatile, with approximately 40% by weight remaining as black residue in the inlet tube after pyrolysis, and secondly, much of the pyrolysate produced was insoluble, polymeric material.

In general it can be seen that Meldrum's acid derivatives produced from 5-membered ring cyclic amides, 6-membered ring cyclic amides and cyclic ureas behave quite differently when subjected to flash vacuum pyrolysis. A variety of factors such as the sp^2 hybridisation of the pyrolysis dipolar intermediate(s) and the susceptibility of the pyrolysis product(s) to autoxidation play a significant part in the pyrolysis outcomes, and this area is one which could be developed and investigated further in the future.

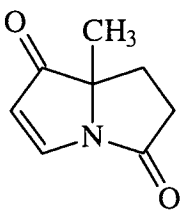
3. Reactions of 7a-Methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione and Related Compounds

(a) 7a-Methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione

Much work has been published in the literature[95] examining the chemistry of a variety of substituted pyrrol-3(2*H*)-ones which have the basic structure **242**, and these compounds are structurally very similar to the left-hand ring of the pyrrolizinedione compound **210**.



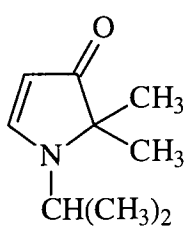
242



210

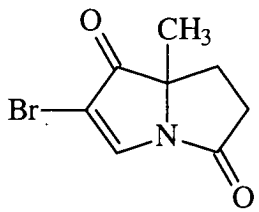
However in the pyrrolizinedione, the nitrogen atom is directly attached to a carbonyl moiety making an amide-type linkage; this could be expected to affect the reactivity of the molecule by having an electron-withdrawing effect on the nitrogen atom's lone pair.

A variety of reactions were carried out with the pyrrolizinedione and comparisons were drawn with 2,2-dimethyl-*N*-isopropylpyrrolone **243** prepared[90] and studied[148,149] by McNab and Monahan.



243

Reaction of the pyrrolizinedione with *N*-bromosuccinimide produced compound **244**, brominated at the 6-position. The ^{1}H NMR spectrum showed the disappearance of the doublet at 5.56 p.p.m. (due to the H(6) proton in the starting material) and the appearance of a singlet at 8.28 p.p.m. (due to the H(5) proton in the product).



244

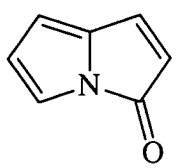
However, the electrophilic substitution was extremely slow, with a reaction time of 48 h giving a yield of only 27% of **244** after dry flash column chromatography. Pyrrolone **243** brominated at the 4-position in a yield in excess of 85% after a 24 h reaction,[149] showing it to be much more reactive toward electrophiles.

Further evidence for the low level of reactivity of the pyrrolizinedione **210** towards electrophiles was obtained by attempting to react it with 5-methoxymethylidene Meldrum's acid. Pyrrolone **243** reacts at the 4-position[149] in a yield of 73% after only a 2 h reaction at room temperature whereas the pyrrolizinedione failed to react at all, even after prolonged heating under reflux in acetonitrile.

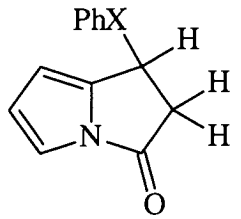
Pyrrolone **243** proved to be inert to nucleophiles, although it was possible to abstract the proton at the 5-position with a strong base to produce an anion (provided position 4 was substituted with highly electronegative group, e.g. Cl, Br).[149]

Previous work[150] with pyrrolizin-3-one **245**, similar in structure to the pyrrolizinedione showed it to be reactive toward nucleophiles. For example, with

thiophenol or aniline, reaction took place across the 1,2-double bond to give the Michael addition compounds **246a** and **246b** respectively.



245

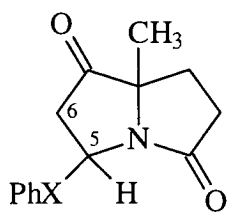


246

(**a**) X = S
(**b**) X = NH

In contrast to the pyrrolone, and in line with the pyrrolizin-3-one reactions described, the pyrrolizinedione system proved to be reactive towards nucleophiles, providing an avenue into a rich area of chemistry.

Reaction of the pyrrolizinedione **210** with thiophenol generated the Michael addition product **247a** in a respectable yield of 64%. Similarly, reaction with aniline produced compound **247b**, in an excellent yield of 89%; both reactions required reaction times of 24 h at room temperature.



247

(**a**) X = S
(**b**) X = NH

Product identities were established by NMR spectroscopy; the two characteristic doublets of H(5) and H(6) in the starting material disappeared, and a doublet of doublets appeared at a high chemical shift of approximately 5.9 p.p.m. due to the H(5) proton in the product. This proton coupled to the two diastereotopic protons on C(6) with coupling constants of 8.5 and 1.7 Hz. One of the C(6) protons was also

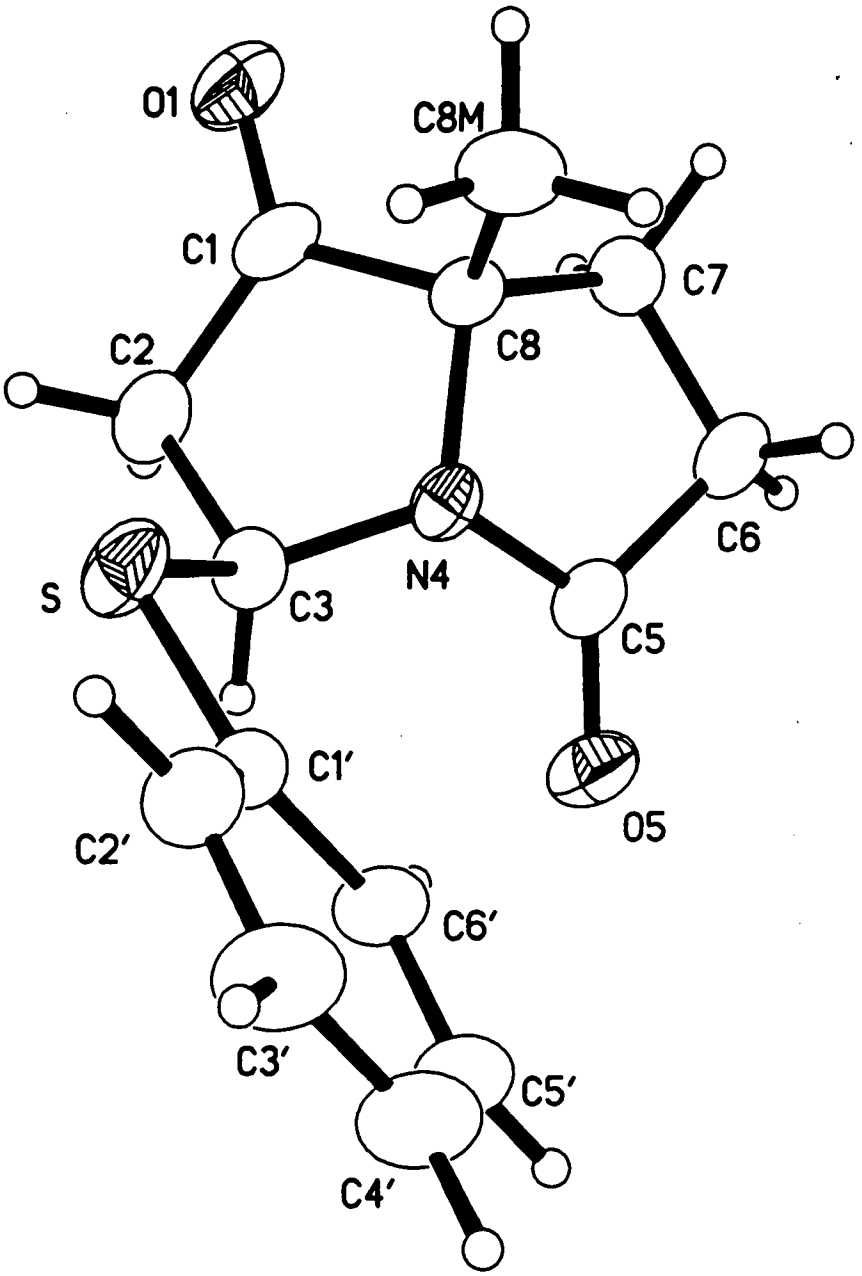
distinguishable as an individual multiplet - a doublet of doublets, with a large geminal coupling of 19.5 Hz and a smaller vicinal coupling of 8.5 Hz to H(5).

Only one set of signals was observed for each of the three protons on C(5) and C(6) indicating only one diastereomer had been formed. A selection of n.O.e. experiments on compound **246a** also indicated this, but enhancements were quite low (~1%) so an X-ray structure was obtained for confirmation.

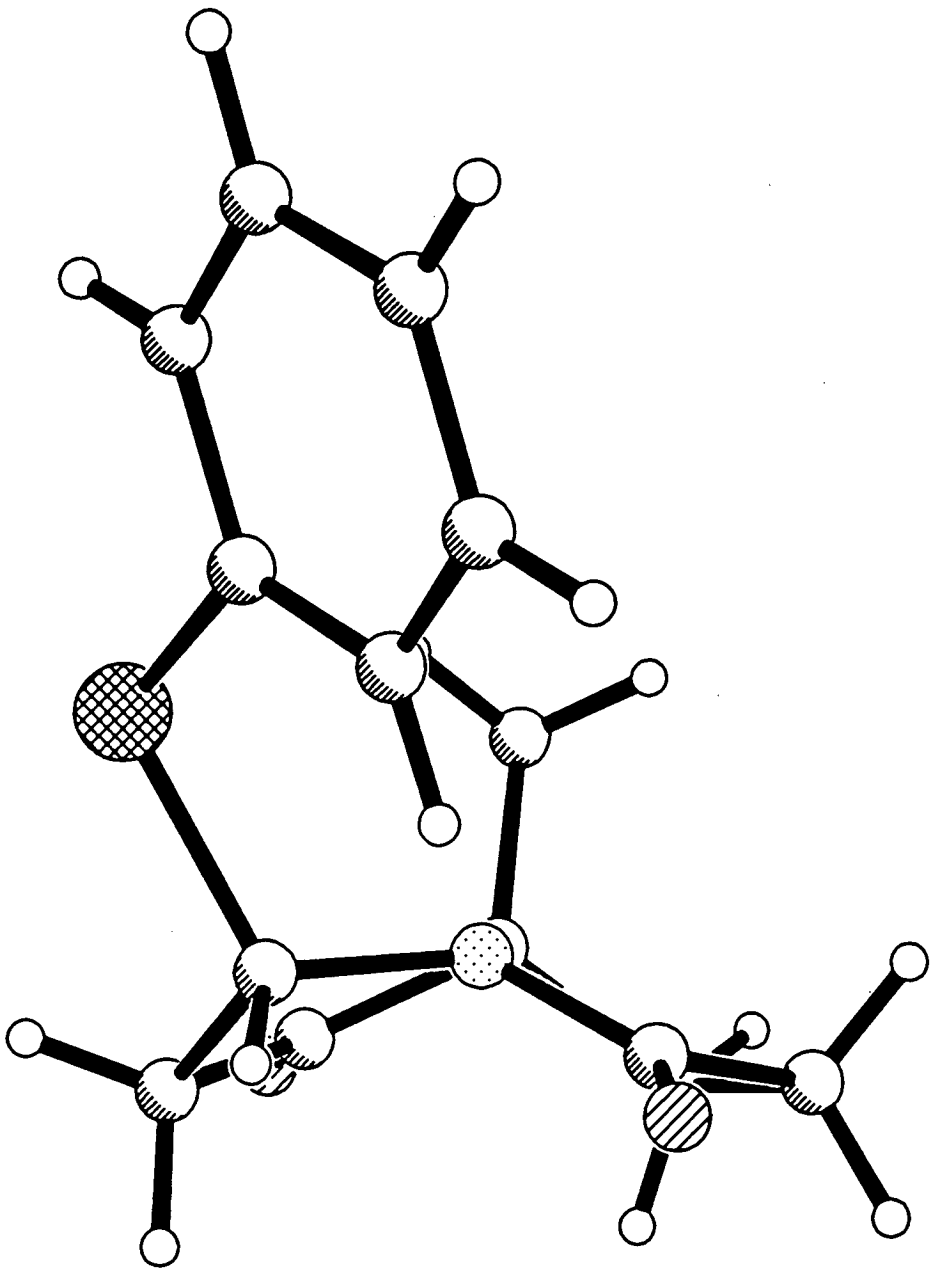
The structure obtained is illustrated in **Schemes 64** and **65** which show above and side views respectively. Bond lengths, bond angles and torsion angles are given in **Tables 29**, **30** and **31** respectively. The X-ray confirmed the orientation of the thiophenyl and methyl substituents with respect to each other and the ring system.

The formation of one diastereomer only may be due to any approach to the underside of the ring system in the starting material being sterically hindered due to its "butterfly-shaped" geometry, as discussed previously (see page 146).

The C(2)-C(3) bond is now fully saturated, and this is reflected in the bond length of 1.547(7) Å [compared with the C(2)-C(3) bond length in the pyrrolizinedione **210** of 1.336(3) Å]. The nitrogen atom is consequently unable to delocalise its lone pair into the left-hand ring, resulting in longer C(3)-N(4) and C(1)-C(2) bonds [1.446(6) Å and 1.509(7) Å respectively] compared with the starting material [1.385(2) Å and 1.447(2) Å respectively], and a larger C(3)-N(4)-C(8) angle [113.3(4)° in the product [compared with 109.58(13)° in the starting material].



Scheme 64



Scheme 65

Table 29 - Bond Lengths (Å)

C(1)-O(1)	1.201(6)
C(1)-C(2)	1.509(7)
C(1)-C(8)	1.515(7)
C(2)-C(3)	1.547(7)
C(3)-N(4)	1.446(6)
C(3)-S	1.839(5)
C(1')-S	1.758(5)
C(1')-C(6')	1.390(6)
C(1')-C(2')	1.399(7)
C(2')-C(3')	1.370(8)
C(3')-C(4')	1.384(7)
C(4')-C(5')	1.374(7)
C(5')-C(6')	1.375(7)
N(4)-C(5)	1.382(6)
N(4)-C(8)	1.465(6)
C(5)-O(5)	1.224(6)
C(5)-C(6)	1.508(7)
C(6)-C(7)	1.517(7)
C(7)-C(8)	1.555(6)
C(8)-C(8M)	1.515(7)

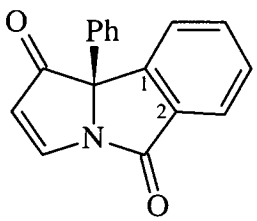
Table 30 - Bond Angles (degrees)

O(1)-C(1)-C(2)	126.0(5)
O(1)-C(1)-C(8)	124.6(5)
C(2)-C(1)-C(8)	109.3(4)
C(1)-C(2)-C(3)	104.8(4)
N(4)-C(3)-C(2)	102.3(4)
N(4)-C(3)-S	115.5(4)
C(2)-C(3)-S	106.2(3)
C(1')-S-C(3)	103.7(2)
C(6')-C(1')-C(2')	119.4(5)
C(6')-C(1')-S	124.9(4)
C(2')-C(1')-S	115.6(4)
C(3')-C(2')-C(1')	119.9(5)
C(2')-C(3')-C(4')	120.4(5)
C(5')-C(4')-C(3')	119.9(5)
C(4')-C(5')-C(6')	120.7(5)
C(5')-C(6')-C(1')	119.8(4)
C(5)-N(4)-C(3)	125.0(4)
C(5)-N(4)-C(8)	112.7(4)
C(3)-N(4)-C(8)	113.3(4)
O(5)-C(5)-N(4)	125.7(4)
O(5)-C(5)-C(6)	126.9(4)
N(4)-C(5)-C(6)	107.4(4)
C(5)-C(6)-C(7)	103.8(4)
C(6)-C(7)-C(8)	103.3(4)
N(4)-C(8)-C(8M)	113.6(4)
N(4)-C(8)-C(1)	102.4(4)
C(8M)-C(8)-C(1)	109.9(4)
N(4)-C(8)-C(7)	103.4(3)
C(8M)-C(8)-C(7)	113.4(4)
C(1)-C(8)-C(7)	113.6(4)

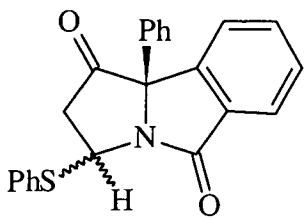
Table 31 - Torsion Angles (degrees)

O(1)-C(1)-C(2)-C(3)	-167.0(5)	C(3)-N(4)-C(5)-C(6)	154.5(4)
C(8)-C(1)-C(2)-C(3)	13.5(5)	C(8)-N(4)-C(5)-C(6)	9.9(5)
C(1)-C(2)-C(3)-N(4)	-24.6(5)	O(5)-C(5)-C(6)-C(7)	153.8(5)
C(1)-C(2)-C(3)-S	96.9(4)	N(4)-C(5)-C(6)-C(7)	-25.8(5)
N(4)-C(3)-S-C(1')	-69.3(4)	C(5)-C(6)-C(7)-C(8)	30.7(5)
C(2)-C(3)-S-C(1')	178.0(3)	C(5)-N(4)-C(8)-C(8M)	-113.5(5)
C(3)-S-C(1')-C(6')	-9.7(5)	C(3)-N(4)-C(8)-C(8M)	97.6(5)
C(3)-S-C(1')-C(2')	173.0(4)	C(5)-N(4)-C(8)-C(1)	128.1(4)
C(6')-C(1')-C(2')-C(3')	1.2(8)	C(3)-N(4)-C(8)-C(1)	-20.8(5)
S-C(1')-C(2')-C(3')	176.2(4)	C(5)-N(4)-C(8)-C(7)	9.8(5)
C(1')-C(2')-C(3')-C(4')	0.7(8)	C(3)-N(4)-C(8)-C(7)	-139.1(4)
C(2')-C(3')-C(4')-C(5')	-0.4(9)	O(1)-C(1)-C(8)-N(4)	-176.5(4)
C(3')-C(4')-C(5')-C(6')	0.5(8)	C(2)-C(1)-C(8)-N(4)	3.1(5)
C(4')-C(5')-C(6')-C(1')	-1.0(8)	O(1)-C(1)-C(8)-C(8M)	62.5(6)
C(2')-C(1')-C(6')-C(5')	1.3(8)	C(2)-C(1)-C(8)-C(8M)	-117.9(5)
S-C(1')-C(6')-C(5')	-175.8(4)	O(1)-C(1)-C(8)-C(7)	-65.7(6)
C(2)-C(3)-N(4)-C5)	-115.3(5)	C(2)-C(1)-C(8)-C(7)	113.9(4)
S-C(3)-N(4)-C(5)	129.8(4)	C(6)-C(7)-C(8)-N(4)	-25.0(5)
C(2)-C(3)-N(4)-C(8)	29.1(5)	C(6)-C(7)-C(8)-C(8M)	98.4(5)
S-C(3)-N(4)-C(8)	-85.8(4)	C(6)-C(7)-C(8)-C(1)	-135.3(4)
C(3)-N(4)-C(5)-O(5)	-25.1(8)	C(8)-N(4)-C(5)-O(5)	-169.7(5)

In a similar system,[151] compound **248** has also been reacted with thiophenol to produce **249**.



248

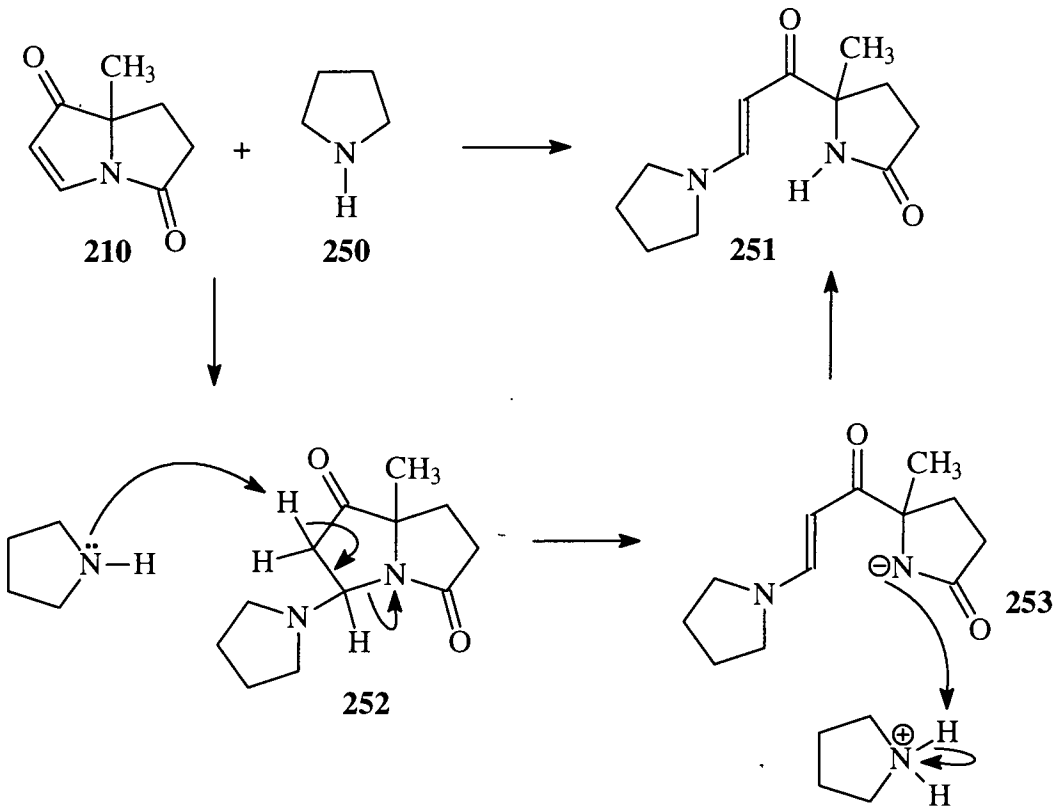


249

In this case, 2 diastereomers were obtained, in a ratio of 3:1 (determined by ^{1}H NMR spectroscopy integrals). The major diastereomer was the compound in which the thiophenol and phenyl substituents were on the same side of the ring (as found for compound **247a**). The minor diastereomer resulted from the attack of thiophenol from the underside of the "butterfly-shaped" system; this may be due to the underside being less crowded due to the absence of downward-pointing protons at the 1 and 2 positions due to the fused benzene ring.

The pyrrolizinedione **210** was also reacted with pyrrolidine **250**, a much stronger base than either the thiophenol or aniline used previously. After a reaction time of 4 h in refluxing methanol ^{1}H NMR spectroscopy showed no starting material to be present.

The product isolated from the reaction was examined by ^{1}H and ^{13}C NMR spectroscopy. This pyrrolidin-2-one compound showed a broad NH signal at 7.40 p.p.m. indicating ring opening had occurred, and doublets at 7.70 p.p.m. and 5.04 p.p.m. with coupling constants of 12.3 Hz, typical of a trans substituted double bond arrangement. The combined ^{1}H, ^{13}C and mass spectroscopic information led to the assignment of structure **251**, the 5,5-disubstituted pyrrolidin-2-one.

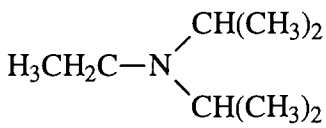


Scheme 66

The product **251** was probably formed *via* the mechanism illustrated in **Scheme 66**. Initially, Michael addition of pyrrolidine across the double bond in **210** formed an intermediate **252**, comparable to the products formed in the previous reactions with thiophenol and aniline. However, pyrrolidine is a much stronger base than either of these two compounds and could subsequently abstract one of the slightly acidic protons of the CH_2 group; which produced the intermediate **253**, which could go on to give the pyrrolidin-2-one product **251** isolated.

Attempts were made at nucleophilic ring opening of the right-hand ring of the pyrrolizinedione **210** compound in order to produce an *N*-unsubstituted pyrrolone. Initial work using sodium methoxide proved unsuccessful, possibly due to the inefficient work-up methods in which products may have been lost. Further work

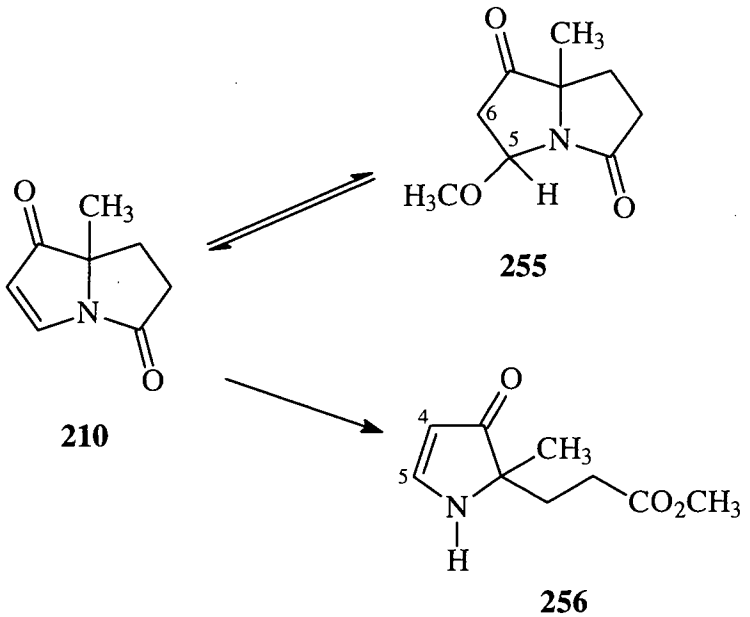
with *t*-butylamine and ethylamine as bases and methanol as solvent gave highly complex mixtures of products. However, reaction with a very soft, sterically hindered base, Hünig's base **254** in methanol gave much more positive results and this was explored in greater detail.



254

The reaction proved to be dependent upon time and temperature. Very short reaction times at room temperature produced, predominantly, the Michael addition product **255**. However, leaving the reaction for longer periods of time, or heating under reflux produced the desired ring opened product, the *N*-unsubstituted pyrrolone **256**.

Both products were identified by NMR spectroscopy. The Michael addition product **255** gave a ^{1}H NMR spectrum similar to those described earlier for compounds **247a** and **247b**, with characteristic patterns for the protons at positions 5 and 6, as well as a singlet due to the methoxy group. The *N*-unsubstituted pyrrolone **246** showed characteristic doublets of doublets at approximately 8 and 5 p.p.m. due to H(5) and H(4) respectively, which couple to each other (^{3}J 4 Hz) and to the proton on the nitrogen (^{3}J 3.4 Hz, ^{4}J 1.4 Hz). The NH showed a characteristically broad signal at 6.7 p.p.m.



In the reaction the initial Michael addition of methoxide was rapid, but reversible due to the presence of base; the hard methoxide nucleophile could go on to attack at the amide type carbonyl carbon atom (a hard centre) to give the irreversible reaction to the pyrrolone **256**.

The extent of the reaction could be monitored by ^{1}H NMR spectroscopy, and various reaction times and ratios of products are given in **Table 32**.

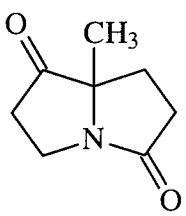
Table 32

Time	Temp (°C)	% **255**	% **256**
5 min	20	94	6
10 min	20	91	9
1 h	20	87	13
24 h	20	24	76
1 h	65	17	83
2 h *	65	0	100

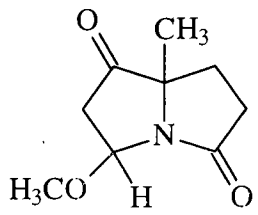
* 2 mole equivalents of Hünig's base used

Reaction times of around 5 minutes were needed in order to isolate the Michael addition product in good yield; the pyrrolone product could be obtained exclusively with a 2 h reaction in refluxing methanol, using two mole equivalents of Hünig's base. The chemistry of the pyrrolone **256** produced is explored later in this chapter (see page 186).

Hydrogenation of the pyrrolizinedione **210** was also successful, producing the fully saturated system **257** in quantitative yield, using 5% palladium on carbon as the catalyst and ethyl acetate as the solvent for the reaction. Under similar sets of conditions, pyrrolone **243** does not hydrogenate.



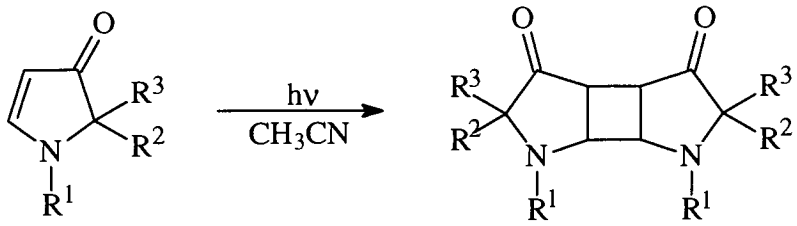
257



255

Use of methanol as the hydrogenation solvent resulted in an alternate reaction taking place and a mixture of two products was obtained. These were shown by ^{1}H and ^{13}C NMR spectroscopy to be the desired product **257** and the methanol addition product **255**, obtained previously.

Previous work in the literature has explored the photochemistry of pyrrolones. Margaretha *et al* [152] photolysed a range of substituted pyrrolones of the form **258** to give the dimeric structures **259**.



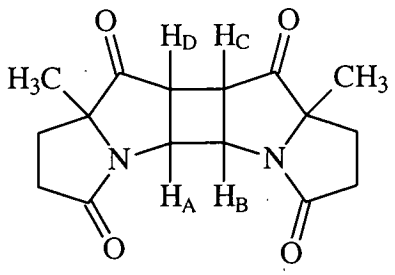
258 **259**

The pyrrolizinedione **210** was photolysed under similar conditions to the pyrrolone above, but after 24 h, only a small amount of the compound was shown to have reacted by ^{1}H NMR spectroscopy. Addition of benzophenone (a triplet sensitiser) to the reaction in catalytic amounts had limited success; however, addition of equimolar amounts gave complete conversion to product(s) within 7 h. Unfortunately, a significant amount of polymer was also produced.

Examination of the soluble products by ^{1}H NMR spectroscopy showed there to be more than one dimer produced, but dry flash column chromatography only succeeded in separating out the benzophenone from the dimers; further spectroscopic examination of this mixture of dimers showed there to be one major product, and two very minor ones. Fractional crystallisation using methanol enabled separation of the major dimer from the remainder and this was subjected to spectroscopic investigations to determine the connectivity and geometry of the compound.

^{13}C NMR spectroscopy (in [$^2H_3$]acetonitrile due to extremely low solubility) showed there to be 16 carbon atom peaks, indicating the molecule was completely unsymmetrical.

^{1}H NMR spectroscopy concentrated on the four cyclobutane ring protons, (labelled H_A, H_B, H_C and H_D in diagram **260**) in order to understand the ^{1}H NMR spectrum and the orientation of these protons with respect to each other.

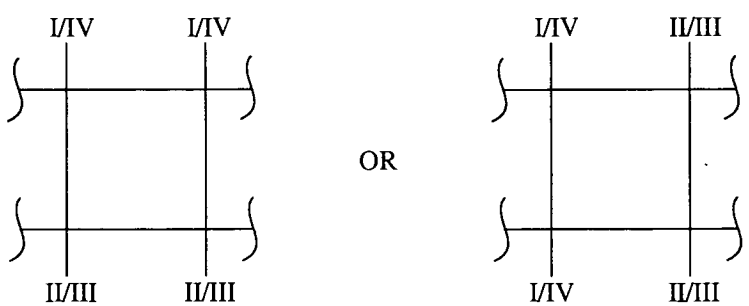


260

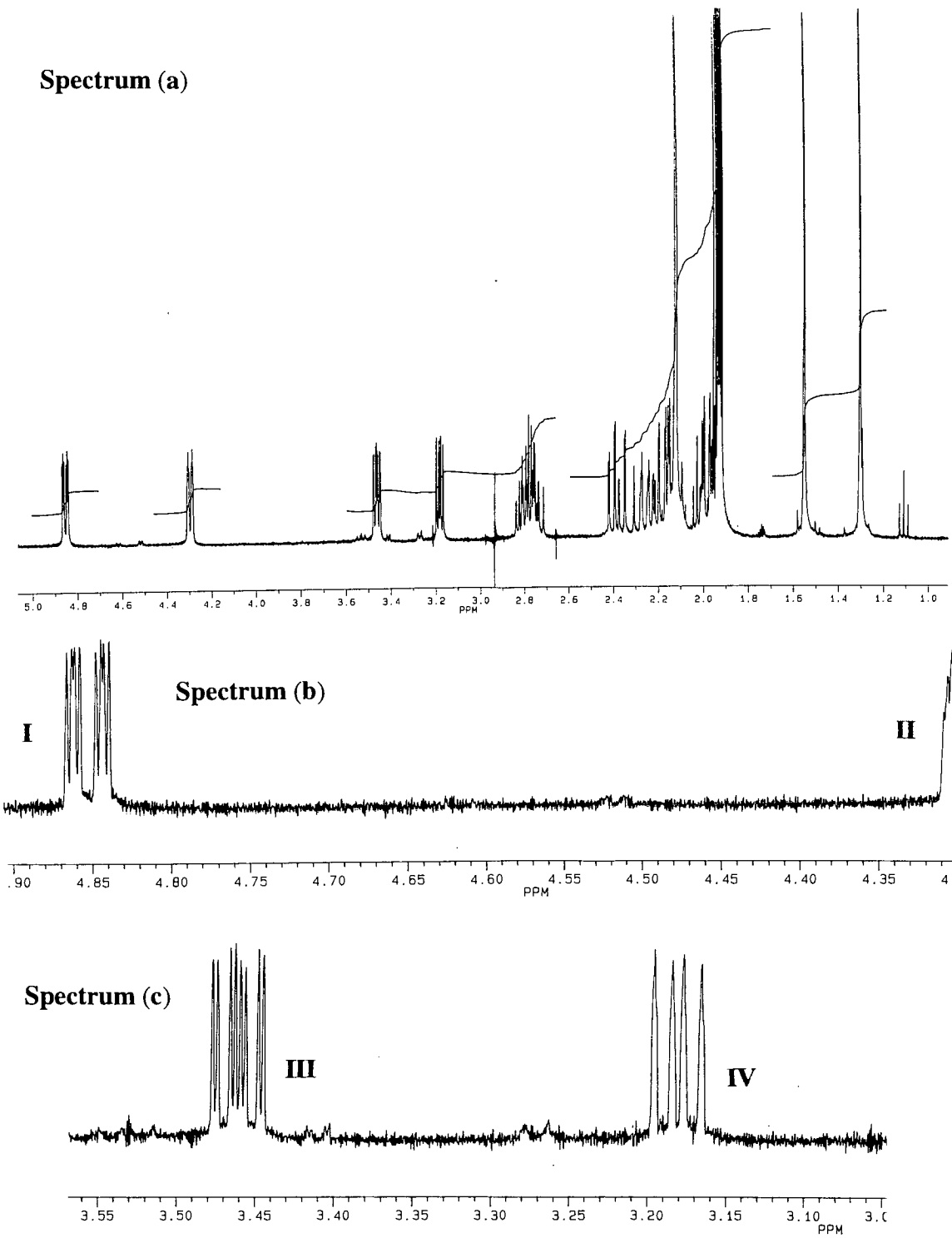
Scheme 67 shows a selection of ^1H NMR spectra relating to compound **260**. All spectra were recorded in [$^2H_3$]acetonitrile and chemical shifts are in p.p.m.

Spectrum 1 shows the complete ^1H NMR spectrum of dimer **260**. **Spectrum 2** shows an expansion of the two cyclobutane protons at higher chemical shifts (4.85 p.p.m. and 4.29 p.p.m.) and **Spectrum 3** shows an expansion of the two cyclobutane protons at lower chemical shifts (3.46 p.p.m. and 3.18 p.p.m.). The four cyclobutane proton signals have been assigned the numerals I, II, III and IV for identification purposes.

Coupling constants for all four signals were examined. Patterns I and IV share a coupling constant of 6.7 Hz and II and III a coupling constant of 6.4 Hz indicating cis arrangements, with I and IV on the same side of the ring and II and III on the same side of the ring, but the opposite side to both I and IV. These two possibilities are shown in **Scheme 68**.



Scheme 68

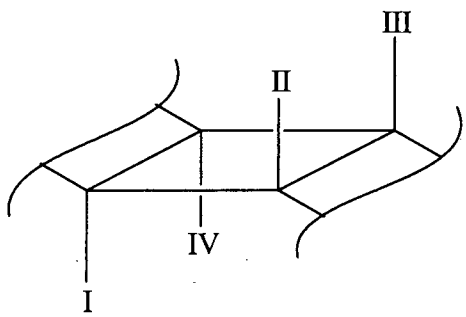

Spectrum (a)
5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
PPM
Spectrum (b)
I
II
.90 4.85 4.80 4.75 4.70 4.65 4.60 4.55 4.50 4.45 4.40 4.35 4.30 4.25
PPM
Spectrum (c)
III
IV
3.55 3.50 3.45 3.40 3.35 3.30 3.25 3.20 3.15 3.10 3.0
PPM

Scheme 67

Second largest coupling constants are shared by I and II and by III and IV, indicating these groups also share sides of the cyclobutane ring, but again the two groups are on opposite sides.

The smallest coupling constants are shared by II and IV and by I and III indicating these protons are diagonally opposite each other, and trans across the ring. All data were confirmed by decoupling experiments.

Combining these pieces of information gives a picture of the cyclobutane ring as shown in **Scheme 69**.

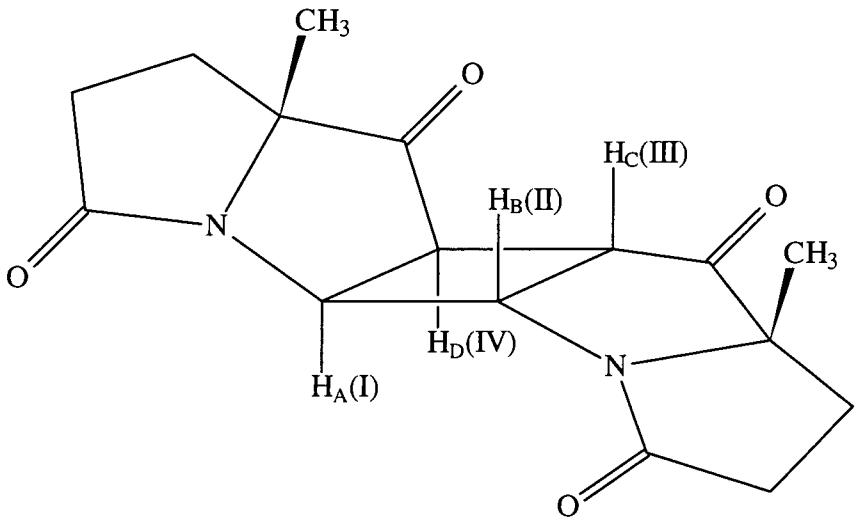


Scheme 69

In order to determine the orientation of this ring in relation to the adjoining rings n.O.e. experiments were carried out. Irradiation of the methyl group at 1.30 p.p.m. gave enhancements of 1% and ½% in II and III respectively, and irradiation of the methyl group at 1.55 p.p.m. gave enhancements of 4% and 3% in II and III respectively. This indicated that both methyl groups were on the same side as the protons giving rise to patterns II and III.

The higher chemical shifts of signals I and II also indicated these two protons were attached to carbon atoms adjacent to the nitrogen atoms in the molecule, and the nitrogen atoms were on the same side, i.e., a head-to-head configuration.

Combining all the information obtained led to the assignment of the structure shown in **Scheme 70**, with signals I, II, III and IV corresponding to protons H_A, H_B, H_C and H_D respectively.



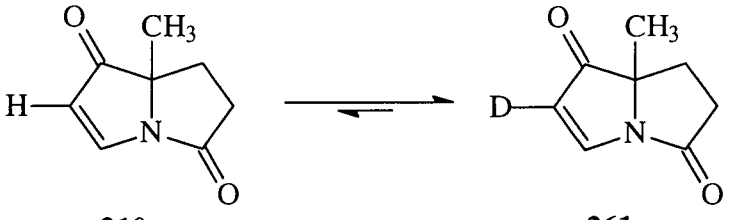
Scheme 70

The decoupling experiments mentioned earlier also revealed more information about H_B (pattern II). Closer examination of this pattern revealed it was more complex than the doublet of doublet of doublets seen for H_A, H_C and H_D. The fine coupling was confirmed as a long range (5 bond) coupling to the CH_2 multiplet at 2.78 p.p.m.; this was the only cyclobutane ring proton for which this phenomenon was observed (at 360 MHz).

The minor amount of the two minor dimers produced proved to be inseparable; examination of the ^1H and ^{13}C NMR spectra of the mixture showed them both to be

symmetrical dimers, again with head-to-head configurations, but no further information could be determined.

The pyrrolizinedione **210** was reacted with deuteriated trifluoroacetic acid. The reaction was monitored over a period of weeks by ^{1}H NMR spectroscopy for exchange of the proton at C(6) for a deuterium atom, to give compound **261**.



210 **261**

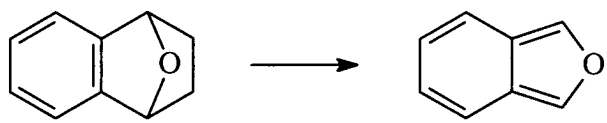
After 4 weeks, 83% deuterium incorporation was observed at C(6) by NMR spectroscopy. Leaving the reaction for longer periods of time resulted only in decomposition. This reaction was much slower than that of pyrrolone **243**[148] which underwent exchange at C(4) in excess of 90% within minutes of mixing to give compound **262**.

243 **262**

Pyrrolone **243** also undergoes rapid and complete protonation at the carbonyl oxygen when reacted with trifluoroacetic acid.[148] This can be monitored by ^{1}H and ^{13}C NMR spectroscopy, as significant chemical shift changes occur upon protonation (see page 188 for further details). Pyrrolizinedione **210** showed no evidence of

protonation (at either carbonyl) after examination by NMR spectroscopy, again showing it to be less reactive. No further change had occurred after 1 week at room temperature

Reaction of the pyrrolizinedione with isobenzofuran[153] was also unsuccessful. Isobenzofuran **264**, generated by flash vacuum pyrolysis using a cold finger trap[154] from 1,4-epoxy-1,2,3,4-tetrahydronaphthalene **263** failed to react with compound **210**, producing only polymeric material after a 3 h reaction at room temperature.

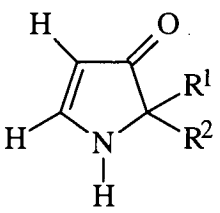


263 **264**

The pyrrolizinedione **210** has been shown to undergo a variety of reactions, producing a wide range of new and interesting products. Its reactivity was shown to be significantly affected by the carbonyl group adjacent to the nitrogen atom, due to removal of electron density from the enamine system due to delocalisation of the nitrogen lone pair into this carbonyl group. The compound was consequently less reactive to electrophiles and more reactive towards nucleophiles than a comparable pyrrolone system.

(b) 2-Methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one

A selection of reactions were performed on the pyrrolone **256** prepared in the previous section. This compound is of particular interest as there are very few examples of 1,4,5-unsubstituted pyrrolones in the literature and little is known about their chemistry. Work by Margaretha *et al* with compounds **265a**,[155] **265b**[156] and **265c**[157] has resulted in detailed photochemical information, but this was the only avenue explored.



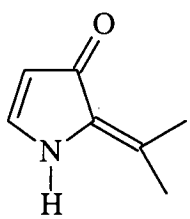
265

(**a**) $R^1 = CH_3, R^2 = CH_3$

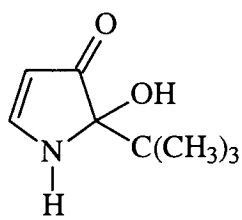
(**b**) $R^1 = CH_3, R^2 = COCH_2CH_3$ (=O)

(**c**) $R^1 = CH_2CH{=}CH_2, R^2 = COCH_2CH_3$ (=O)

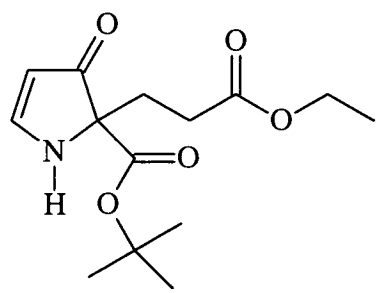
Other pyrrolones known of this substitution pattern include compounds **266**,[158] **267**[159] and **268**,[160] but again their chemistry is relatively unexplored, often due to them being produced in very low yields, or as unwanted reaction by-products.



266



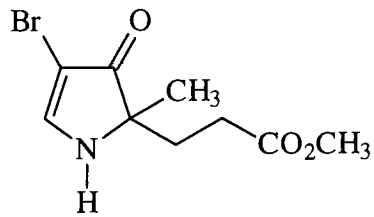
267



268

Reaction of the pyrrolone with *N*-bromosuccinimide was successful, with the product **269** (brominated at the 4-position) being isolated in a yield of 50% after a 24 h

reaction and subsequent work-up. The product was identified by ^{1}H NMR spectroscopy; disappearance of the doublet at 5 p.p.m. and conversion of the doublet at 8 p.p.m. to a singlet indicated bromination had been successful at C(4).

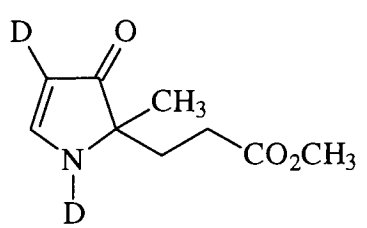


269

Yields were still lower than those obtained with the model pyrrolone **243**[149] (~85%), but the reaction was significantly improved when compared to the pyrrolizinedione discussed previously.

Reaction of the pyrrolone with thiophenol was unsuccessful; monitoring the reaction by ^{1}H NMR spectroscopy showed only unreacted starting materials after 24 h at room temperature. Moderation of the electron-donating nitrogen atom by introducing an electron-withdrawing group at the 1-position may facilitate a Michael type addition reaction.

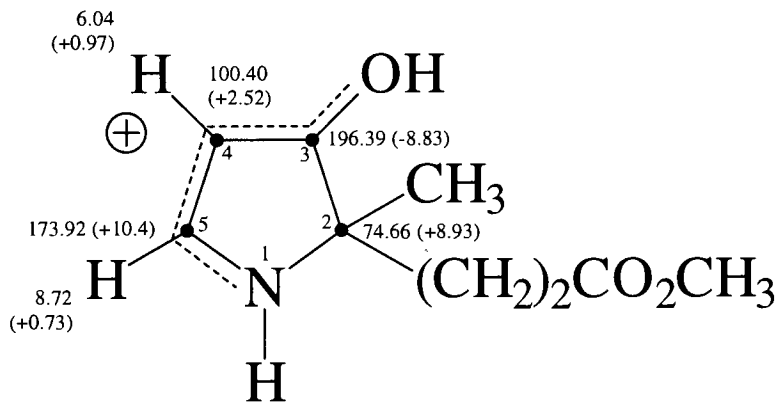
Allowing the pyrrolone to stand in deuteriated trifluoroacetic acid resulted in exchange of the protons at C(4) and N(1) to give compound **270**.



270

Deuterium incorporation was observed at C(4) (94%) after 15 min, in excellent agreement with the comparable reaction of the model pyrrolone **243**[148] which underwent exchange in excess of 90% within minutes of mixing.

Reaction with trifluoroacetic acid also proved successful, with the carbonyl oxygen atom being rapidly protonated; this was observed by ^{1}H and ^{13}C monitoring of the sample. **Scheme 71** illustrates the chemical shifts of a selection of proton and carbon atoms in the protonated pyrrolone, with figures in p.p.m. Numbers in brackets show the differences between the chemical shifts of the protonated and unprotonated forms; the sign indicates the direction of the shift, e.g. "+" indicates a higher chemical shift in the protonated form compared to the unprotonated form.

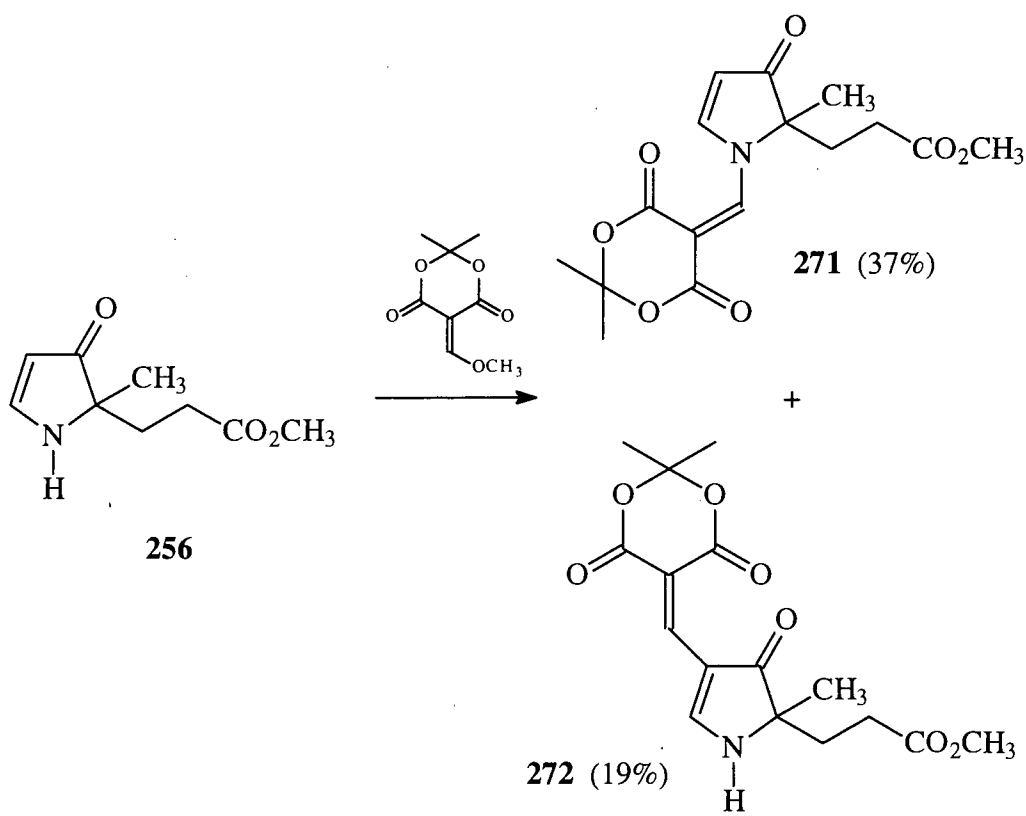


Scheme 71

Upon protonation in the model pyrrolone **243**, the chemical shifts of H(4), H(5), C(2), C(3), C(4) and C(5) changed significantly.[148] The C(3) signal was shielded by approximately 12 p.p.m. (despite the effect of the positive charge) due to a reduction of the anisotropic effect of the carbonyl group on *O*-protonation. The other signals quoted above were all deshielded to varying degrees, with the greatest effect being observed at C(5) (approximately 8 p.p.m.), a site of low electron density, and the least at C(4) (approximately 2 p.p.m.), a site of high electron density.

The results obtained for pyrrolone **256** shown in **Scheme 71** were entirely consistent with the observations for the model pyrrolone **243**. The chemical shift of C(3) was reduced by 8.83 p.p.m. due to the shielding effect of protonation at this site. Large increases of 10.4 p.p.m. in the C(5) chemical shift and 8.93 p.p.m. in the C(2) chemical shift contrasted with the small effect protonation had on C(4) (+2.52 p.p.m.). Both H(4) and H(5) were deshielded significantly.

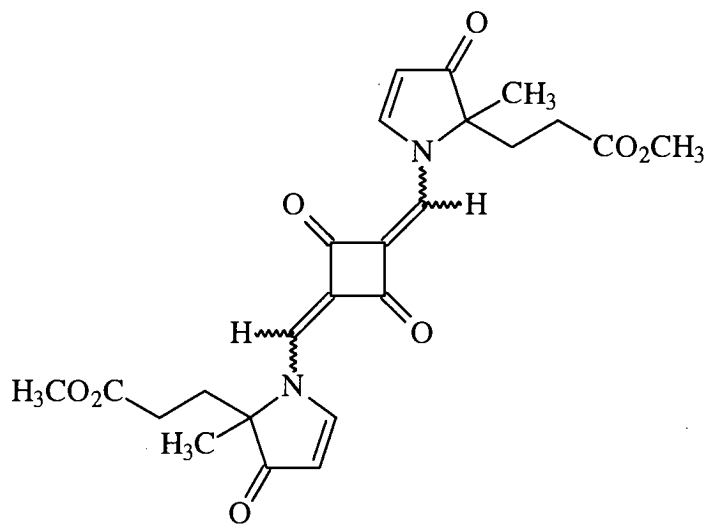
Pyrrolone **256** was also reacted with 5-methoxymethylidene Meldrum's acid. Unlike the model pyrrolone **243** which is *N*-substituted, two sites of reaction were available, namely C(4) and N(1), and two products were obtained after column chromatography of the reaction products.



Examination of the separated products by NMR spectroscopy led to the assignment of compounds **271** and **272**, with twice the amount of the *N*-substituted product being produced compared to the C(4) substituted product. There was no evidence for the 1,4-disubstituted product being produced. The ^{1}H NMR spectrum of **271** showed the 4 and 5 positions of the pyrrolone ring to be unsubstituted, with 2 sets of doublets at 9.73 p.p.m. and 5.93 p.p.m., with coupling constants of 4.4 Hz; the disappearance of the NH signal and its couplings to H(4) and H(5) indicated the pyrrolone was *N*-substituted. In the ^{1}H NMR spectrum of compound **272** the signal for H(4) was missing, indicating substitution at this position of the pyrrolone ring. The H(5) signal appeared as a doublet due to coupling to the NH. In both compounds the characteristic signals from the Meldrum's acid ring were present, i.e. a singlet at ~1.7 p.p.m. integrating to six protons and a singlet at ~8 p.p.m. due to the methine proton.

Both of the Meldrum's acid derivatives produced were pyrolysed. The pyrolysate from the *N*-substituted pyrrolone **271** contained a significant amount of polymeric material. The minor soluble portion was examined by ^{1}H NMR spectroscopy and thin layer chromatography; these techniques indicated a mixture. Dry flash column chromatography succeeded in separating out two compounds, but in very small yields of only 6% and 7%. The first compound was examined by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The latter technique indicated a molecular weight of *m/z* 235 and spectroscopy indicated 12 carbon atoms and 13 hydrogen atoms; this left a mass of 78 which could correspond to one nitrogen atom and 4 oxygen atoms. The spectra also indicated the pyrrolone nucleus from the starting material was intact, indicating by subtraction the substituent on the nitrogen atom was comprised of the unit C_3HO.

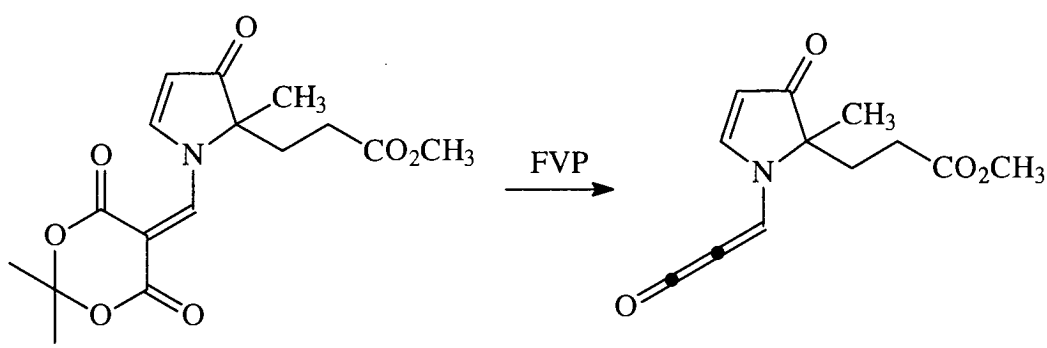
In order to make a feasible structure from the information gathered, a symmetrical compound of *m/z* 470 and formula ($C_{24}H_{26}$ + $C_6H_2O_2$) was considered and is shown as compound **273**.



273

This symmetrical molecule fits all the data collected by NMR spectroscopy and could be expected to produce a molecular ion of ½M by cleaving symmetrically across the cyclobutane-1,3-dione ring.

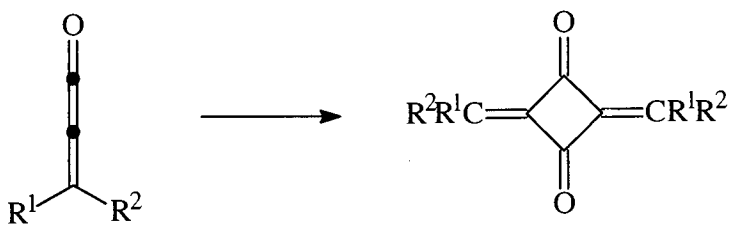
Consideration of the pyrolysis intermediate **274** produced also indicates an alternative reaction may be occurring.



271 **274**

Methylideneketene **274** has very few options open, with the usual hydrogen shift mechanism unavailable to the molecule; consequently dimerisation is a viable alternative to produce dimer **273**.

This phenomenon is not unprecedented in the literature. Early work by Brown *et al*[161] highlighted the generation of methylideneketenes of the type **275a-d**.



275 **276**

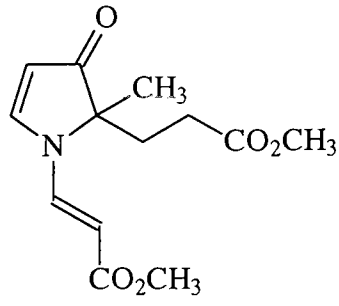
(**a**) $R^1 = Ph$ $R^2 = H$
(**b**) $R^1 = R^2 = Ph$
(**c**) $R^1 = R^2 = CH_3$
(**d**) $R^1 = C(CH_3)_3$ $R^2 = H$

(**a**) $R^1 = Ph$ $R^2 = H$
(**b**) $R^1 = R^2 = Ph$
(**c**) $R^1 = R^2 = CH_3$
(**d**) $R^1 = C(CH_3)_3$ $R^2 = H$

All four methylideneketene molecules dimerised to the cyclobutane-1,3-dione compounds **276a-d**, in some cases in yields in excess of 90% and all were highly coloured (red and orange compounds). However, in contrast to these colourful compounds which showed significant visible absorptions in the range 390-460 nm, compound **273** was obtained as a brown oil and showed no significant ultraviolet absorptions, perhaps casting a doubt on the assignment of the structure **273** shown.

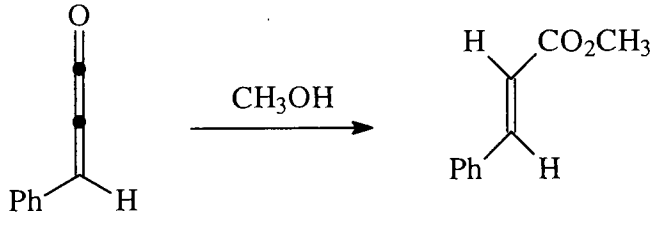
The second product isolated from the pyrolysate by chromatography was present in such a small amount that ^{13}C NMR spectrometry was not possible due to the weakness of the NMR sample. ^1H NMR spectroscopy indicated the original pyrrolone unit was again intact but with the NH signal absent indicating substitution

at the nitrogen atom, and also the presence of a trans substituted vinyl group containing an ester moiety. This information indicated structure **275**, and mass spectrometry gave the correct molecular ion for this formula (*m/z* 267).



277

Brown *et al* [161] also reported the formation of vinyl esters from methylideneketenes; for example molecule **275a** could be trapped with methanol vapour during FVP to give the vinyl ester **278**.



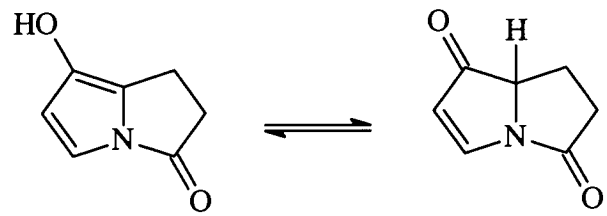
275a **278**

It is not impossible that the intermediate from the pyrolysis of compound **271** could have been trapped by traces of methanol during the procedure, so giving rise to the trace amounts of the *N*-vinyl substituted pyrrolone **277**.

Pyrolysis of the 4-substituted pyrrolone **272** generated a large amount of polymeric material; examination of the very minor soluble portion by ^{1}H NMR spectroscopy showed no identifiable peaks in an extremely weak spectrum.

(c) 1,2-Dihydro-7-hydroxypyrrolizin-3(3*H*)-one

The pyrrolizinone **212** isolated was also of interest in terms of its chemistry. Possible tautomerisation to compound **211** meant it could react *via* the hydroxypyrrole or pyrrolone tautomer and these two have quite different chemistry.



212 **211**

Areas of interest include possible autoxidation of the system and chemistry of the electron rich hydroxypyrrole ring, for example, reactions with electrophiles, alkylation and also ring opening reactions. Comparisons can also be drawn to the chemistry of the pyrrolizinedione **210** and the pyrrolone **243** discussed previously.

Unfortunately, although compound **212** could be isolated quite easily, attempts to carry out chemistry on this were, in the most part, unsuccessful.

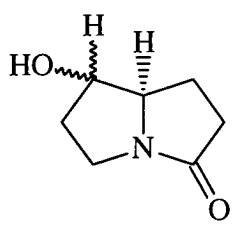
Reaction with *N*-bromosuccinimide resulted only in decomposition. The pyrrolizinone also failed to react with 5-methoxymethylidene Meldrum's acid, even after extended periods heating under reflux in acetonitrile, with unreacted starting material always recovered.

Attempts to ring open the pyrrolizinone compound with Hünig's base, as described previously, produced highly complex mixtures; ^{1}H NMR spectroscopy showed no

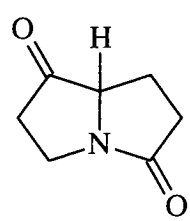
evidence of starting material in the mixtures, but no identifiable products could be isolated.

Attempted methylation of the hydroxyl group on C(7) using a sodium hydride and methyl *p*-toluenesulfonate combination[102] was unsuccessful, giving only decomposition.

Hydrogenation using palladium on charcoal and methanol was successful in terms of reducing the double bonds in the left-hand ring to give a fully saturated system. However, two products were always produced in the reaction which were inseparable by dry flash column chromatography, namely compounds **279** and **280**. These compounds were identified by ^{1}H and ^{13}C NMR spectroscopy of the mixture.

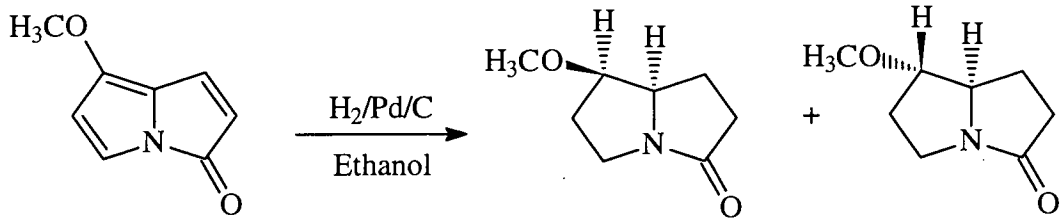


279



280

Due to the complexity of the ^{1}H NMR spectrum of the mixture, it was not possible to determine which diastereoisomer of **279** had been formed. However, work[154] on a similar compound **281**, under almost identical conditions gave a mixture of diastereomers which could be identified; this work is illustrated in **Scheme 72**.

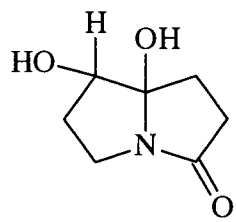


281 **282** **283**

Scheme 72

The two products formed, **282** and **283**, were determined to be in the ratio 6:1, indicating the diastereomer with the two hydrogen atoms cis to one another was the favoured product.

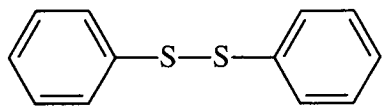
A further complication of the hydrogenation of the pyrrolizinone **212** was the air sensitivity of the compound prior to the procedure. If the solvent used was not thoroughly degassed, varying amounts of the autoxidised, reduced product **284** were also produced in addition to compounds **282** and **283**, again illustrating the sensitivity of an unsubstituted ring junction carbon atom to autoxidation. Again, any intermediate radical formed with the radical on the ring junction carbon atom would be captodative, which would provide extra stability.



284

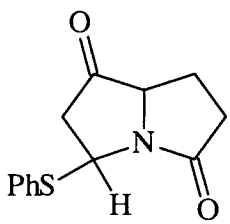
Reaction of the pyrrolizinone **212** with thiophenol was also successful, but again produced a mixture of products, which were separated by dry flash column chromatography. The first product isolated was identified as phenyldisulfide **285**, a

predictable product when thiophenol is used in a reaction (especially if autoxidation *via* radicals is occurring).

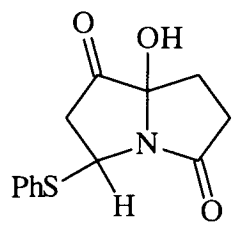


285

The second and third products **286** and **287** isolated had both successfully undergone Michael addition at C(5); however, with the ring junction now vulnerable with a proton at this position, the third product had also undergone autoxidation at the ring junction, further reinforcing the results described previously.



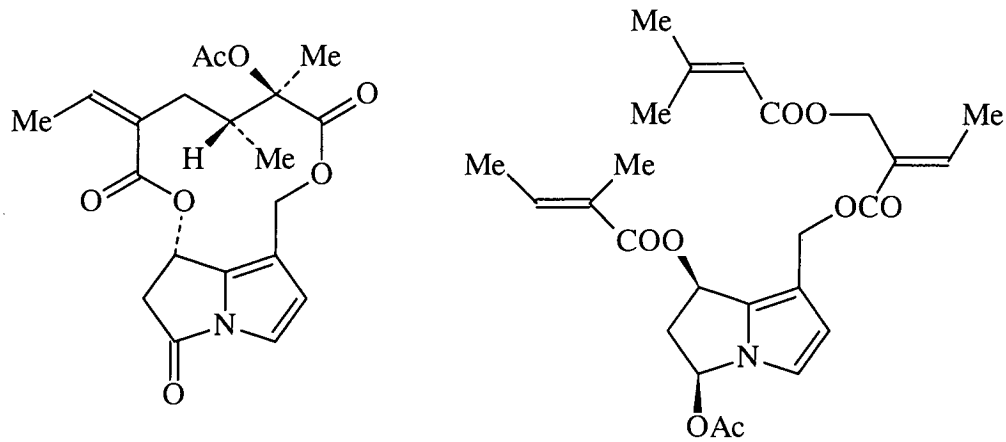
286



287

In general, autoxidation proved to be a problem in reactions with pyrrolizinone **212**, but it was possible to perform hydrogenation and Michael addition reactions with some degree of success.

The core skeleton of this compound has many similarities to naturally occurring pyrrolizidine alkaloids,[162] two examples of which are shown in **Scheme 73**.



Scheme 73

Future work optimising reaction conditions and developing the chemistry of the pyrrolizinone system could provide avenues into in the rapidly expanding area of pyrrolizidine alkaloids.

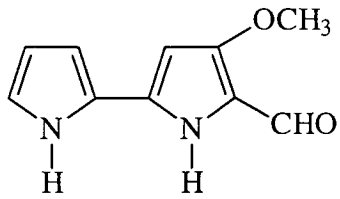
D. PREPARATION OF PRODIGIOSIN ANALOGUES

As discussed in the Introduction, the toxicity of prodigiosin precludes its use as a therapeutic agent, but it, and other members of the prodigiosin family have shown high levels of biological activity, for example, the use of undecylprodigiosin as an immunosuppressant.[73] Consequently there is a need for analogues which could potentially be less toxic but still have high levels of activity.

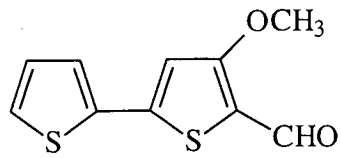
Ongoing work[74] at Kanazawa University, Japan, in the Department of Biochemistry is examining the inhibition of proton pump activity of lysosomal $H^{\oplus}$-ATPase by a variety of compounds, with particular interest in compounds from, and analogous to, the prodigiosin family. Structure-activity relationships are an important feature of this research; replacement of various functional groups or atoms in the prodigiosin skeleton may provide information on lead compounds with similar or greater activity compared to prodigiosin itself, but more importantly, lower levels of toxicity.

The work described in this chapter concentrates on varying the heteroatoms in all three rings of the prodigiosin skeleton, varying the substituent patterns on Ring C, and introducing Ring C moieties that could alter the hydrogen bonding regime in the prodigiosin analogues. In addition, all analogues prepared were subjected to biological testing at Kanazawa University, as part of their ongoing program of work described above.

Previous work in this area by McNab *et al* [87,96] utilised the technique of FVP to prepare prodigiosin analogues. Intermediate **288**, containing the heteroatom sulfur, and directly analogous to the methoxybipyrrole carboxaldehyde **5** used to prepare prodigiosin, was prepared by FVP.

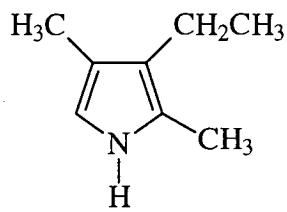


5

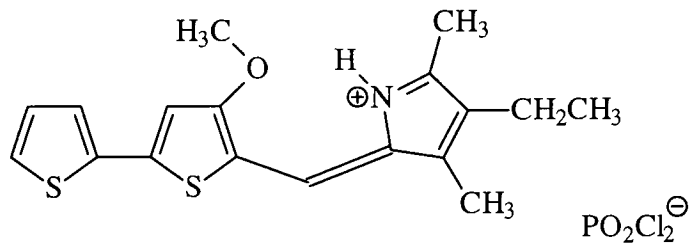


288

This compound could then be coupled to an appropriate Ring C compound to produce an analogue of prodigiosin; McNab *et al* [87] coupled the intermediate to commercially available kryptopyrrole **289** to produce the analogue **85a** as a salt.



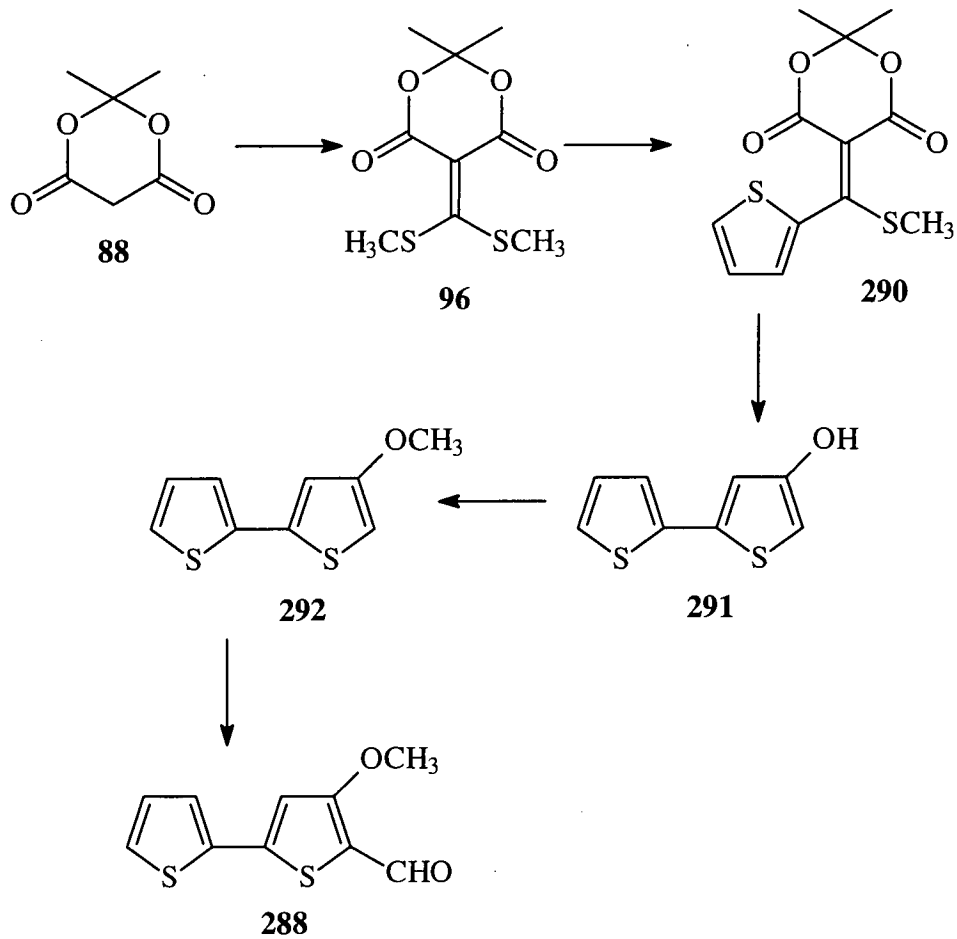
289



85a

Many other analogues could be prepared by this route by varying the Ring C compound used; these analogues could be more closely related to naturally occurring compounds in the prodigiosin family by using Ring C molecules such as 2-methyl-3-pentylpyrrole (as in prodigiosin itself) or 2-undecylpyrrole (as in undecylprodigiosin).

In order to produce other analogues, the A-B ring system **288** was prepared, following the previous procedure;[96,87] this is illustrated in detail in **Scheme 74**.



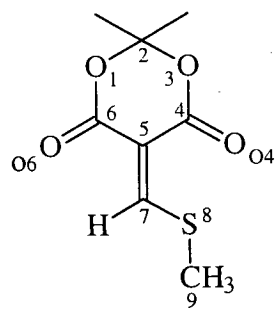
Scheme 74

The bismethylsulfanyl compound **96** was prepared from Meldrum's acid **88**, carbon disulfide and methyl iodide in a moderate yield of 46%. Selective replacement of one of the SCH_3 groups *via* a Grignard reaction with thiophen-2-yl magnesium bromide produced compound **290** in a 96% yield. This compound was then pyrolysed at 625 °C to generate the bithiophene compound **291** (in an almost quantitative yield) as a highly crystalline solid. Methylation[102] at the oxygen atom using a combination of sodium hydride, methyl *p*-toluene sulfonate and dimethyl-imidazolidinone (as solvent) successfully gave **292** in a 68% yield; finally, this compound was formylated[163] at the 2-position using Vilsmeier conditions to give the desired intermediate **288**, in a good yield of 82%. Formylation occurred exclusively

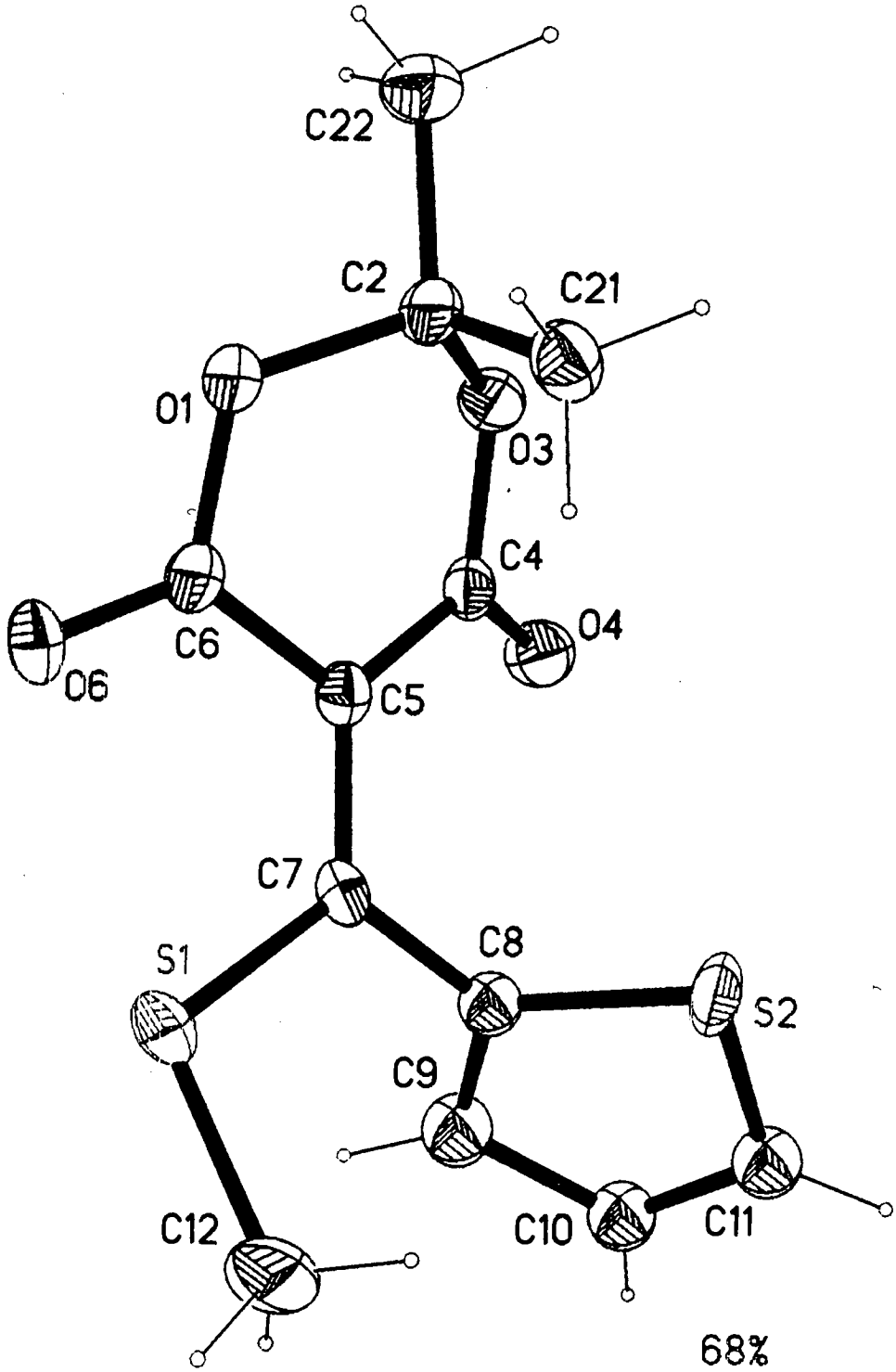
at this position; the conjugating electron-donating effect of the methoxy substituent increased the reactivity of the α-position.

A crystal structure of the methylsulfanylthienyl intermediate **290** was obtained,[164] and this is illustrated in **Schemes 75** and **76** with associated bond lengths, bond angles and torsion angles in **Tables 33**, **34** and **35** respectively. As the structures in the two schemes show, the compound was found to be disordered with two different orientations of the thiophene ring, occurring in an approximate ratio of 2 (**Scheme 75**) : 1 (**Scheme 76**).

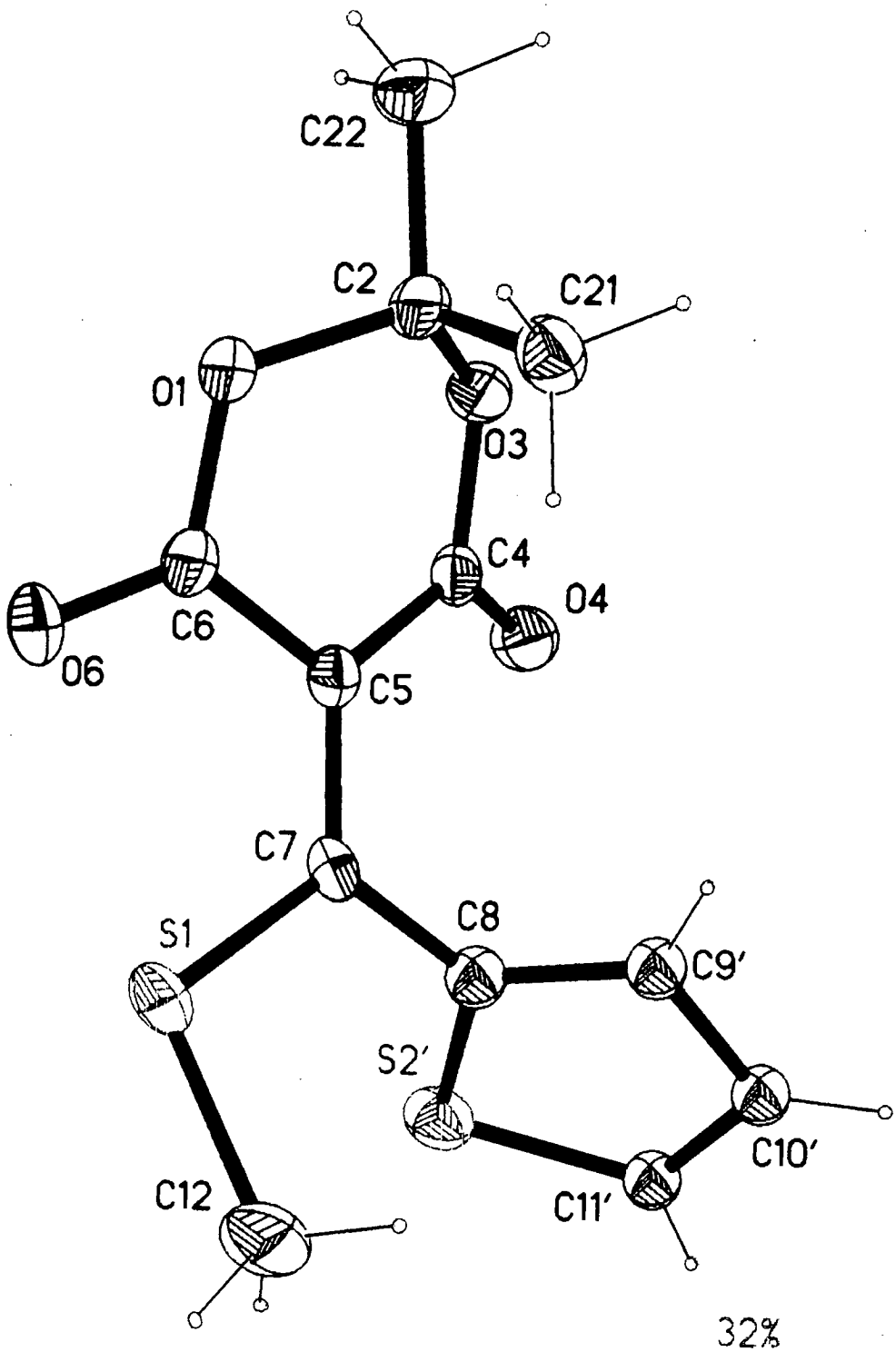
The crystal structure of a similar compound **293** has been reported in the literature,[119] and this potentially provided an opportunity to observe the effect on the structure of replacing the methylene H-atom with a substituent.



293



Scheme 75



Scheme 76

Table 33 - Bond Lengths (Å)

O(1)-C(6)	1.365(5)
O(1)-C(2)	1.443(5)
C(2)-O(3)	1.435(4)
C(2)-C(21)	1.508(5)
C(2)-C(22)	1.513(5)
O(3)-C(4)	1.355(4)
C(4)-O(4)	1.223(4)
C(4)-C(5)	1.472(5)
C(5)-C(7)	1.377(5)
C(5)-C(6)	1.472(5)
C(6)-O(6)	1.207(5)
C(7)-C(8)	1.473(5)
C(7)-S(1)	1.744(4)
S(1)-C(12)	1.817(5)
C(8)-C(9´)	1.372(8)
C(8)-S(2)	1.670(4)
C(9)-C(10)	1.466(12)
C(10)-C(11)	1.362(7)
C(11)-S(2)	1.719(7)
C(8)-C(9´)	1.377(9)
C(8)-S(2´)	1.660(6)
C(9´)-C(10´)	1.475(14)
C(10´)-C(11´)	1.362(9)
C(11´)-S(2´)	1.722(9)

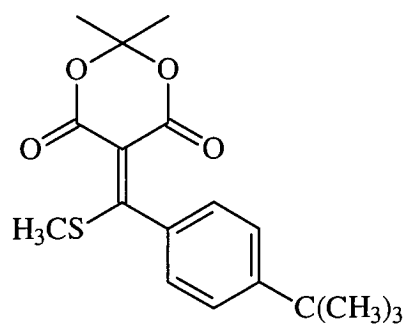
Table 34 - Bond Angles (degrees)

C(6)-O(1)-C(2)	117.7(3)
O(1)-C(2)-O(3)	108.7(3)
O(1)-C(2)-C(21)	111.1(3)
O(3)-C(2)-C(21)	111.1(3)
O(1)-C(2)-C(22)	105.7(3)
O(3)-C(2)-C(22)	106.8(3)
C(21)-C(2)-C(22)	113.1(3)
C(4)-O(3)-C(2)	118.5(3)
O(4)-C(4)-O(3)	118.0(3)
O(4)-C(4)-C(5)	125.0(3)
O(3)-C(4)-C(5)	116.8(3)
C(7)-C(5)-C(4)	123.4(3)
C(7)-C(5)-C(6)	120.8(3)
C(4)-C(5)-C(6)	115.6(3)
O(6)-C(6)-O(1)	118.4(3)
O(6)-C(6)-C(5)	124.7(3)
O(1)-C(6)-C(5)	116.8(3)
C(8)-C(7)-C(5)	122.0(3)
C(5)-C(7)-S(1)	121.2(3)
C(8)-C(7)-S(1)	116.8(2)
C(7)-S(1)-C(12)	104.1(2)
C(9)-C(8)-C(7)	124.1(5)
C(9)-C(8)-S(2)	113.7(5)
C(7)-C(8)-S(2)	122.0(2)
C(8)-C(9)-C(10)	111.2(7)
C(11)-C(10)-C(9)	110.1(5)
C(10)-C(11)-S(2)	113.2(4)
C(8)-S(2)-C(11)	91.6(3)
C(9´)-C(8)-C(7)	122.3(6)
C(9´)-C(8)-S(2´)	113.7(5)
C(7)-C(8)-S(2´)	124.0(3)
C(8)-C(9´)-C(10´)	111.5(8)
C(11´)-C(10´)-C(9´)	109.3(7)
C(10´)-C(11´)-S(2´)	113.7(7)
C(8)-S(2´)-C(11´)	91.8(4)

Table 35 - Torsion Angles (degrees)

C(6)-O(1)-C(2)-C(3)	50.4(4)	C(2)-O(1)-C(6)-O(6)	167.5(3)
C(6)-O(1)-C(2)-C(21)	-72.2(4)	C(2)-O(1)-C(6)-C(5)	-14.7(4)
C(6)-O(1)-C(2)-C(22)	164.8(3)	C(7)-C(5)-C(6)-O(6)	-19.8(5)
O(1)-C(2)-O(3)-C(4)	-50.4(4)	C(4)-C(5)-C(6)-O(6)	154.6(3)
C(21)-C(2)-O(3)-C(4)	72.1(4)	C(7)-C(5)-C(6)-O(1)	162.6(3)
C(22)-C(2)-O(3)-C(4)	-164.1(3)	C(4)-C(5)-C(6)-O(1)	-23.0(4)
C(2)-O(3)-C(4)-O(4)	-170.6(3)	C(4)-C(5)-C(7)-C(8)	9.7(5)
C(2)-O(3)-C(4)-C(5)	14.4(4)	C(6)-C(5)-C(7)-C(8)	-176.4(3)
O(4)-C(4)-C(5)-C(7)	22.9(5)	C(4)-C(5)-C(7)-S(1)	-173.2(2)
O(3)-C(4)-C(5)-C(7)	-162.5(3)	C(6)-C(5)-C(7)-S(1)	0.7(4)
O(4)-C(4)-C(5)-C(6)	-151.3(3)	C(5)-C(7)-S(1)-C(12)	-160.5(3)
O(3)-C(4)-C(5)-C(6)	23.4(4)	C(8)-C(7)-S(1)-C(12)	16.8(3)
C(5)-C(7)-C(8)-C(9)	-120.3(8)	S(1)-C(7)-C(8)-C(9)	62.4(8)
C(5)-C(7)-C(8)-S(2)	65.2(4)	S(1)-C(7)-C(8)-S(2)	-112.0(3)
C(7)-C(8)-C(9)-C(10)	-177.6(5)	S(2)-C(8)-C(9)-C(10)	-2.7(11)
C(8)-C(9)-C(10)-C(11)	4.1(12)	C(9)-C(10)-C(11)-S(2)	-3.8(9)
C(9)-C(8)-S(2)-C(11)	0.5(7)	C(7)-C(8)-S(2)-C(11)	175.5(3)
C(10)-C(11)-S(2)-C(8)	2.0(5)	C(5)-C(7)-C(8)-C(9´)	64.2(12)
S(1)-C(7)-C(8)-C(9´)	-113.1(12)	C(5)-C(7)-C(8)-S(2´)	-117.9(4)
S(1)-C(7)-C(8)-S(2´)	64.8(4)	C(7)-C(8)-C(9´)-C(10´)	176.7(9)
S(2´)-C(8)-C(9´)-C(10´)	-1(2)	C(8)-C(9´)-C(10´)-C(11´)	0(2)
C(9´)-C(10´)-C(11´)-S(2´)	2(2)	C(9´)-C(8)-S(2´)-C(11´)	1.9(12)
C(7)-C(8)-S(2´)-C(11´)	-176.1(5)	C(10´)-C(11´)-S(2´)-C(8)	-2.1(10)

However, the two-fold rotational disorder observed in the substituent of **290** provided a problem such that this phenomenon affected the ability to measure accurately the bond lengths, bond angles, etc. Consequently the crystal structure of a similar compound **294**, the *p*-*t*-butylphenyl substituted derivative[96] was obtained to aid comparisons between sets of data.

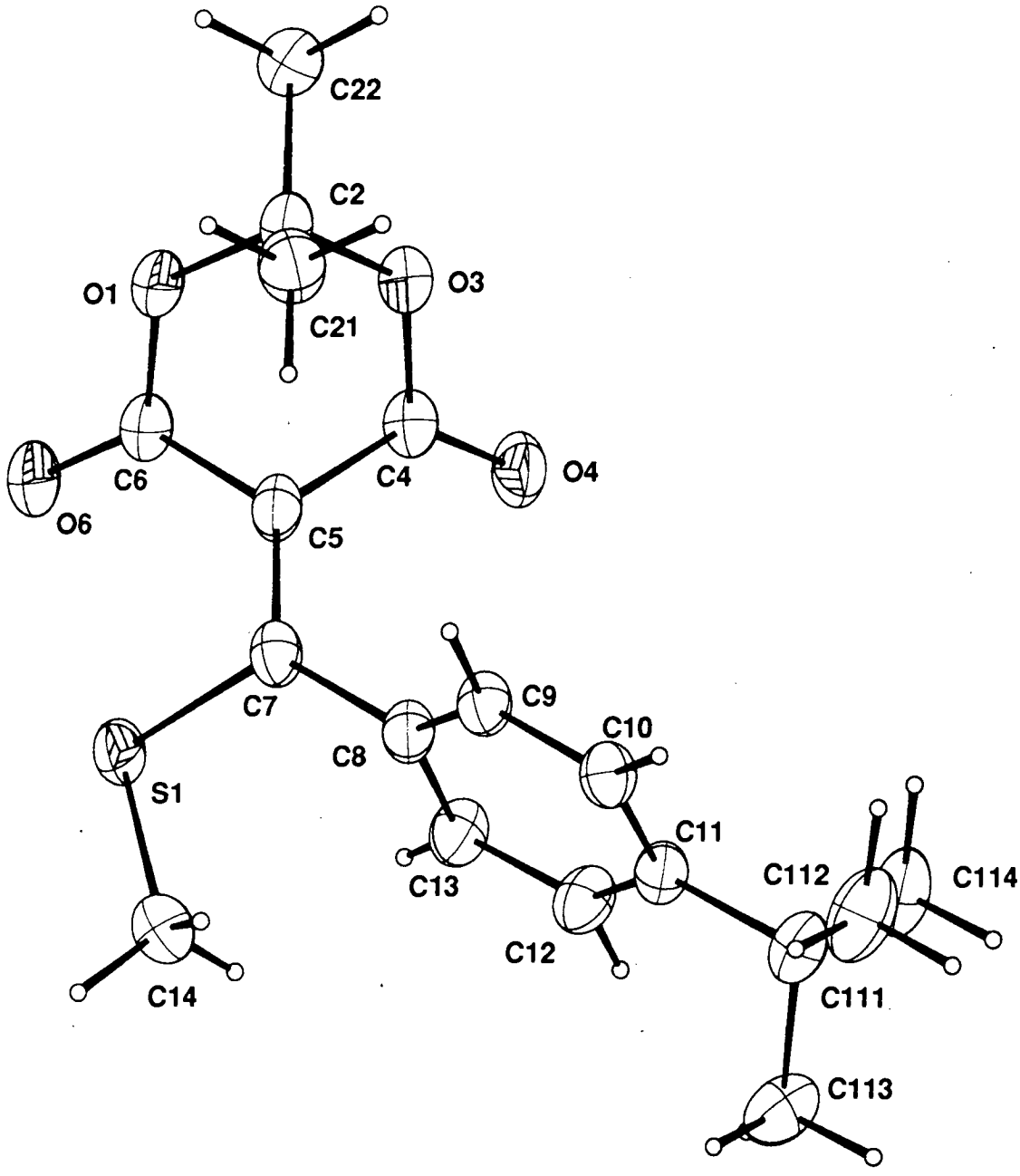


294

The crystal structure of compound **294** is illustrated in **Scheme 77** with associated data in **Tables 36**, **37** and **38**.

This second derivative cannot exhibit any rotational disorder, and examination of the structure along with that of compound **290** enabled comparisons to be made to the monosubstituted compound **293**.

In both of the disubstituted compounds there is the possibility of electron-donation from the additional ring into the methylidene Meldrum's acid unit, and this is reflected in the large S(1)-C(7) bond length in compounds **290** and **294** [1.744(4) Å and 1.738(1) Å respectively] when compared with compound **293** [1.694(3) Å].


C22
C2
O1
O3
C21
C6
C4
O4
O6
C5
C7
C9
C10
C8
S1
C11
C13
C112
C114
C12
C14
C111
C113

Scheme 77

Table 36 - Bond Lengths (Å)

O(1)-C(6)	1.353(2)
O(1)-C(2)	1.444(2)
C(2)-O(3)	1.436(2)
C(2)-C(21)	1.505(2)
C(2)-C(22)	1.502(2)
O(3)-C(4)	1.353(2)
C(4)-O(4)	1.200(2)
C(4)-C(5)	1.485(2)
C(5)-C(7)	1.368(2)
C(5)-C(6)	1.467(2)
C(6)-O(6)	1.204(2)
C(7)-C(8)	1.488(2)
C(7)-S(1)	1.738(1)
S(1)-C(14)	1.801(2)
C(8)-C(9)	1.388(2)
C(8)-C(13)	1.390(2)
C(9)-C(10)	1.388(2)
C(10)-C(11)	1.390(2)
C(11)-C(12)	1.397(2)
C(11)-C(111)	1.532(2)
C(12)-C(13)	1.384(2)
C(111)-C(112)	1.531(2)
C(111)-C(113)	1.525(2)
C(111)-C(114)	1.533(2)

Table 37 - Bond Angles (degrees)

C(6)-O(1)-C(2)	118.0(1)
O(1)-C(2)-O(3)	108.7(1)
O(1)-C(2)-C(21)	110.8(1)
O(3)-C(2)-C(21)	111.1(1)
O(1)-C(2)-C(22)	106.5(1)
O(3)-C(2)-C(22)	105.7(1)
C(21)-C(2)-C(22)	113.8(1)
C(4)-O(3)-C(2)	119.0(1)
O(4)-C(4)-O(3)	118.3(1)
O(4)-C(4)-C(5)	125.9(1)
O(3)-C(4)-C(5)	115.6(1)
C(7)-C(5)-C(4)	121.6(1)
C(7)-C(5)-C(6)	121.8(1)
C(4)-C(5)-C(6)	116.4(1)
O(6)-C(6)-O(1)	118.3(1)
O(6)-C(6)-C(5)	125.0(1)
O(1)-C(6)-C(5)	116.7(1)
C(8)-C(7)-C(5)	121.3(1)
C(5)-C(7)-S(1)	120.3(1)
C(8)-C(7)-S(1)	118.4(1)
C(7)-S(1)-C(14)	104.94(7)
C(9)-C(8)-C(7)	119.9(1)
C(7)-C(8)-C(13)	121.7(1)
C(9)-C(8)-C(13)	118.3(1)
C(8)-C(9)-C(10)	121.0(1)
C(11)-C(10)-C(9)	121.1(1)
C(10)-C(11)-C(12)	117.5(1)
C(10)-C(11)-C(111)	122.6(1)
C(12)-C(11)-C(111)	119.9(1)
C(11)-C(12)-C(13)	121.5(1)
C(8)-C(13)-C(12)	120.5(1)
C(11)-C(111)-C(112)	112.3(1)
C(11)-C(111)-C(113)	110.0(1)
C(112)-C(111)-C(113)	109.4(1)
C(11)-C(111)-C(114)	108.3(1)
C(112)-C(111)-C(114)	108.1(1)
C(113)-C(111)-C(114)	108.6(1)

Table 38 - Torsion Angles (degrees)

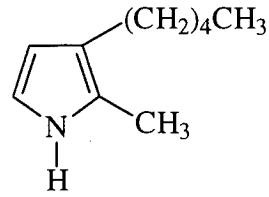
C(14)-S(1)-C(7)-C(5)	-167.78(11)	C(6)-C(5)-C(7)-S(1)	5.32(16)
C(14-S(1)-C(7)-C(8)	29.74(11)	C(6)-C(5)-C(7)-C(8)	-172.12(12)
C(6)-O(1)-C(2)-C(3)	50.52(19)	S(1)-C(7)-C(8)-C(9)	-115.04(16)
C(6)-O(1)-C(2)-C(21)	-71.78(19)	S(1)-C(7)-C(8)-C(13)	65.5(2)
C(6)-O(1)-C(2)-C(22)	163.95(15)	C(5)-C(7)-C(8)-C(9)	62.4(2)
C(2)-O(1)-C(6)-O(6)	166.25(15)	C(5)-C(7)-C(8)-C(13)	-116.97(18)
C(2)-O(1)-C(6)-C(5)	-15.3(2)	C(7)-C(8)-C(9)-C(10)	-179.51(18)
C(4)-O(3)-C(2)-O(1)	-50.60(16)	C(13)-C(8)-C(9)-C(10)	-0.1(3)
C(4)-O(3)-C(2)-C(21)	71.55(16)	C(7)-C(8)-C(13)-C(12)	177.22(18)
C(4)-O(3)-C(2)-C(22)	-164.52(12)	C(9)-C(8)-C(13)-C(12)	-2.2(3)
C(2)-O(3)-C(4)-O(4)	-169.34(11)	C(8)-C(9)-C(10)-C(11)	2.3(3)
C(2)-O(3)-C(4)-C(5)	15.19(15)	C(9)-C(10)-C(11)-C(12)	-2.2(3)
O(3)-C(4)-C(5)-C(6)	22.42(15)	C(9)-C(10)-C(11)-C(111)	176.01(18)
O(3)-C(4)-C(5)-C(7)	-162.58(10)	C(10)-C(11)-C(12)-C(13)	-0.1(3)
O(4)-C(4)-C(5)-C(6)	-162.64(13)	C(111)-C(11)-C(12)-C(13)	-178.35(18)
O(4)-C(4)-C(5)-C(7)	22.36(19)	C(10)-C(11)-C(111)-C(112)	6.7(3)
C(4)-C(5)-C(6)-O(1)	-22.28(18)	C(10)-C(11)-C(111)-C(113)	128.82(19)
C(4)-C(5)-C(6)-O(6)	156.06(15)	C(10)-C(11)-C(111)-C(114)	-112.6(2)
C(7)-C(5)-C(6)-O(1)	162.74(12)	C(12)-C(11)-C(111)-C(112)	-175.16(18)
C(7)-C(5)-C(6)-O(6)	-18.9(2)	C(12)-C(11)-C(111)-C(113)	-53.0(2)
C(4)-C(5)-C(7)-S(1)	-169.41(8)	C(12)-C(11)-C(111)-C(114)	65.5(2)
C(4)-C(5)-C(7)-C(8)	13.15(16)	C(11)-C(12)-C(13)-C(8)	2.3(3)

Electron-donation from both the substituents in compounds **290** and **294** provides some single bond character to C(5)-C(7) [1.377(5) Å and 1.368(2) Å respectively] and some double bond character to both C(5)-C(4) [1.472(5) Å and 1.485(2) Å respectively] and C(5)-C(6) [1.472(5) Å and 1.467(2) Å respectively]; this is consistent with observations from other Meldrum's acid derivative crystal structures with electron-donating substituents;[119] compound **293** showed a C(5)-C(7) bond length of 1.356(4) Å and C(5)-C(4) and C(5)-C(6) bond lengths of 1.454(4) Å and 1.467(4) Å respectively.

The second, bulky ring substituent in compounds **290** and **294** also has an effect on the angle at S1 [104.1(2)° and 104.94(7)° respectively] when compared with the angle at the S atom in compound **293** [100.94(16)°]. This is probably due to steric interaction between the ring substituents and the SCH_3 groups. In accordance with this, the C(5)-C(7)-S(1) angles in compounds **290** and **294** [121.2(3)° and 120.3(1)° respectively] are much smaller than in compound **293** [126.16(3)°], as are the C(4)-C(5)-C(6) angles [115.6(3)° and 116.4(1)° in compounds **290** and **294** compared with 120.2(3)° in compound **293**].

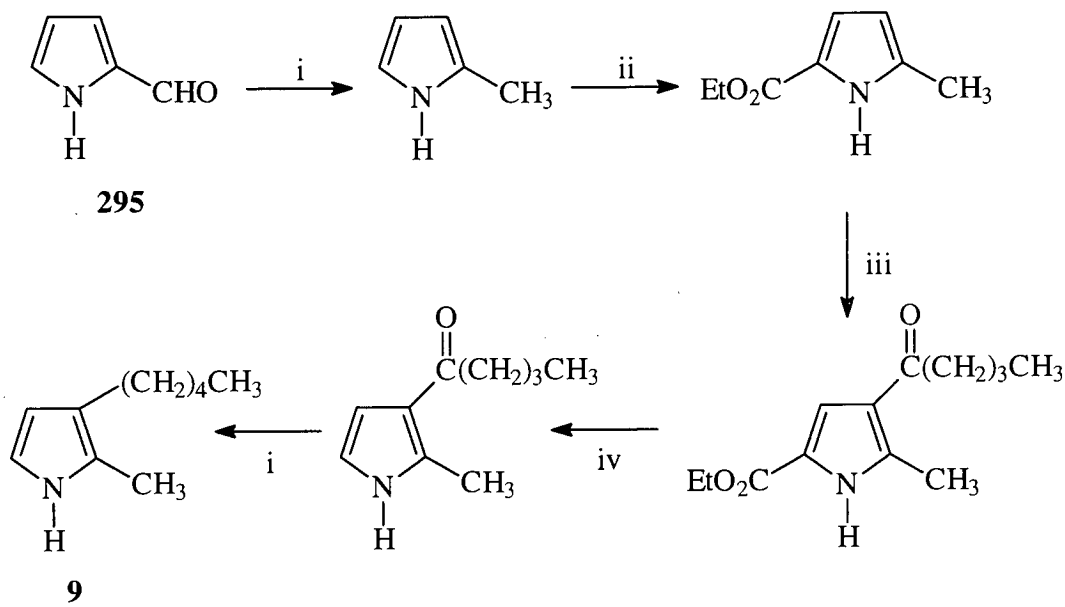
The next stage in the prodigiosin analogue synthesis was to couple the prepared bithiophene compound **288** with an appropriate Ring C compound.

An obvious pyrrole to use would be 2-methyl-3-pentylpyrrole **9** as this forms the Ring C in prodigiosin itself.



9

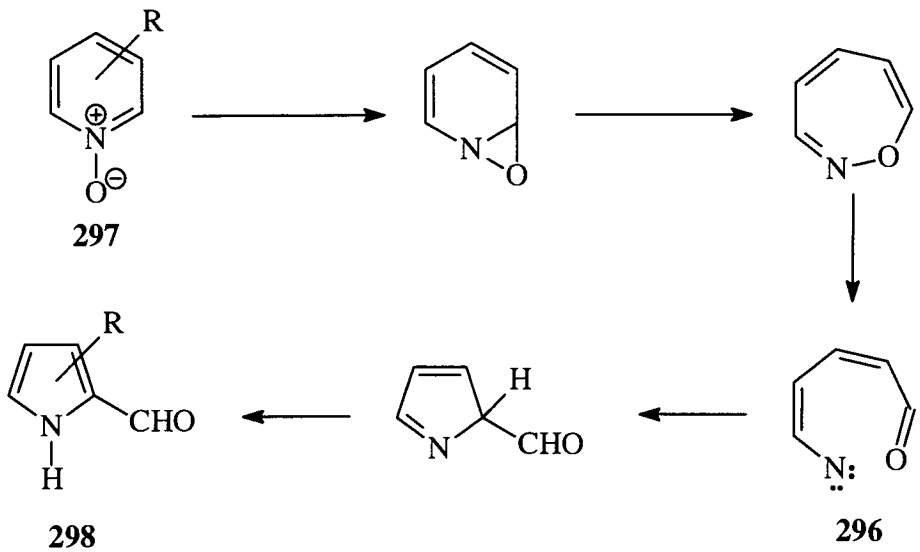
Previous work[61] to prepare this compound started from 2-formylpyrrole **293**. The route taken is shown in **Scheme 78**. However, the overall yield of the route was quite low, particularly due to the second step to incorporate the 5-ethoxycarbonyl group, with a yield of only 35%.



Reagents and Conditions: i, H_2NNH_2, KOH, ethylene glycol, heat; ii, CH_3CH_2MgBr, CH_3CH_2OCOCl; iii, $CH_3(CH_2)_3COCl$, $AlCl_3$; iv, KOH, heat.

Scheme 78

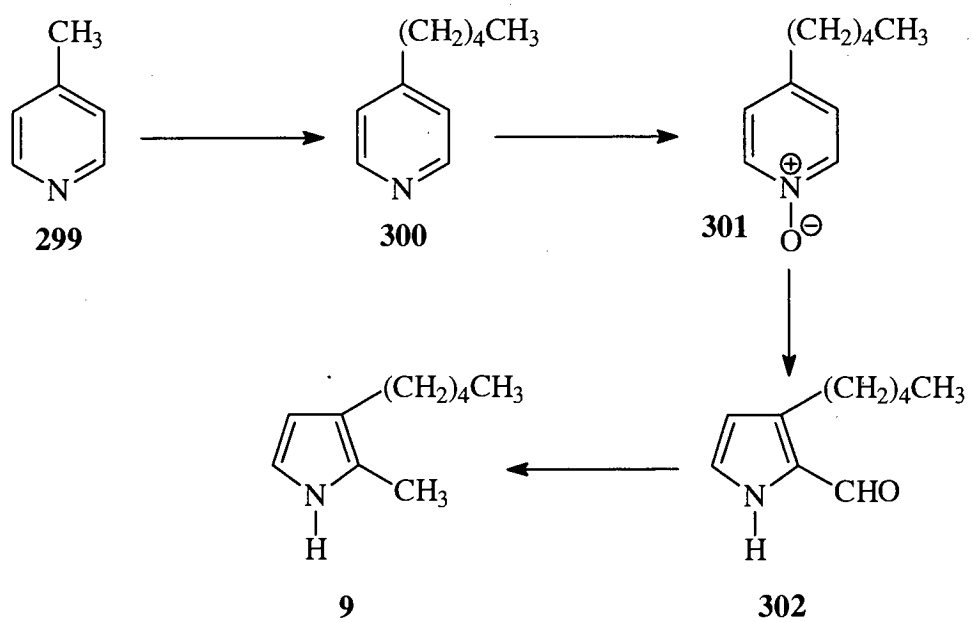
Consequently an alternative route was developed to compound **9**; this involved the key step of photolytic ring contraction[165] of an *N*-oxide to a pyrrole-2-carboxaldehyde, which is thought to occur by the mechanism shown in **Scheme 79**.[165]



Scheme 79

During the photolysis, formation of a nitrene **296** (*via* a seven membered ring) and subsequent cyclisation and tautomerisation enables the overall conversion of a pyridine *N*-oxide compound **297** into a pyrrole-2-carboxaldehyde **298**.

The route developed to 2-methyl-3-pentylpyrrole is illustrated in **Scheme 80**.



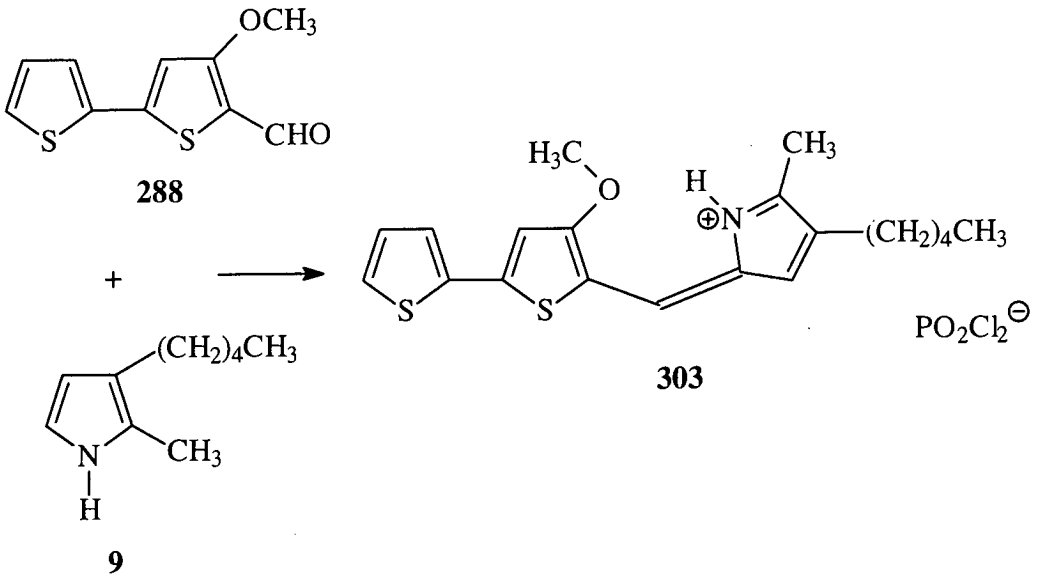
Scheme 80

Commercially available 4-methylpyridine **299** was converted to 4-pentylpyridine **300** *via* a reaction with sodamide and 1-bromobutane[166,167] in an excellent yield of 89%. Preparation of the *N*-oxide **301** also proceeded smoothly[168] in a yield of 93%. To produce the 2,3-disubstituted pyrrole **302** the technique of photolytic ring contraction[165] was employed, as described previously. Applying this reaction to the substituted *N*-oxide **301** successfully produced the disubstituted pyrrole **302**. However, yields were very low, at only 20%, and this yield decreased still further if more than 0.5 g of *N*-oxide was used in the photolysis. The desired product was always isolated by dry flash column chromatography.

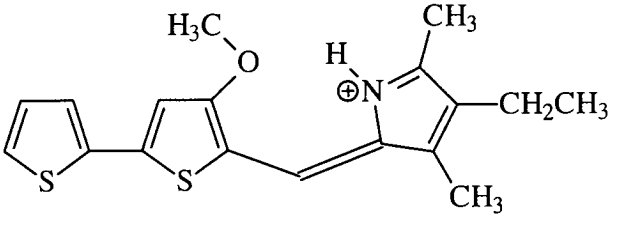
The final step involved reduction of the formyl group; initial work with lithium aluminium hydride produced complex mixtures of products, but Wolff-Kishner conditions[169] successfully produced the desired 2-methyl-3-pentylpyrrole **9**, albeit in a rather low yield of 23%.

The route provided a very direct, regiospecific pathway into 3-substituted pyrrole-2-aldehydes. Unfortunately yields for the ring contraction step were lower than the expected 35-40% from previous literature work.[165] The final step also proved disappointing in terms of yield and future work could look at optimising this reduction of the formyl group.

However, enough of compound **9** was produced to prepare a compound analogous to prodigiosin and the prepared Ring C pyrrole was coupled to the bithiophene system **288**.



The coupling was carried out using conditions developed by van Koeveringe.[170] Phosphoryl chloride was added to a solution of the two precursors **9** and **288** in *n*-pentane to produce the analogue **303** as a hydrodichlorophosphate salt. Previous work[87] produced the salt **85a** as a crystalline solid which precipitated out of the pentane solution within minutes of adding the phosphoryl chloride.



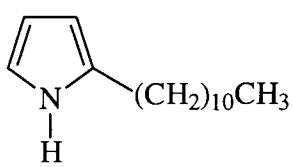
85a

However, in the case of the analogue **303**, no precipitate had formed after 30 min; consequently, the solvent was removed under reduced pressure leaving a thick purple oil that did not solidify. The oil was examined by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry to determine if compound **303** had been successfully produced.

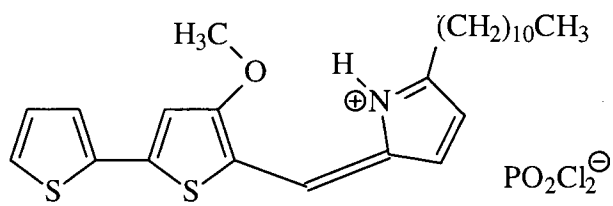
In the starting bithiophene **288** the formyl proton appeared as a singlet at a characteristic chemical shift of ~9.9 p.p.m.; a successful reaction would result in the disappearance of this peak, and the appearance of a singlet due to the methine proton in the range 7.5-8.5 p.p.m. The broad signal due to the NH proton would also be shifted to a much higher δ value, as the nitrogen atom in the product carries a positive charge. Mass spectrometry should also produce a molecular ion corresponding to the cation in the salt.

The ^{1}H NMR spectrum of the oil showed a singlet at 8.13 p.p.m., and a broad peak at 14.15 p.p.m. due to the methine and the NH protons respectively. No singlet was seen at ~9.9 p.p.m. In addition a molecular ion of *m/z* 358 was obtained, corresponding to the cation of compound **303**; this information combined with the rest of the ^{1}H and ^{13}C NMR data, indicated the reaction to produce the prodigiosin analogue **303** had been successful.

Following the success of this reaction, a variety of other prodigiosin analogues were targetted. A second analogue containing a Ring C pyrrole found in a naturally occurring compound was also prepared. 2-Undecylpyrrole **11** was prepared according to the literature method of Wasserman *et al* [26] using pyrrole and 1-undecylbromide in a Grignard reaction to give the desired compound, but in a very low yield of 7%.



11

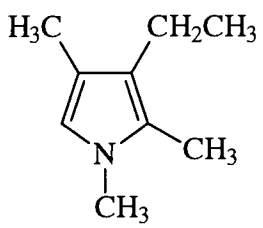


304

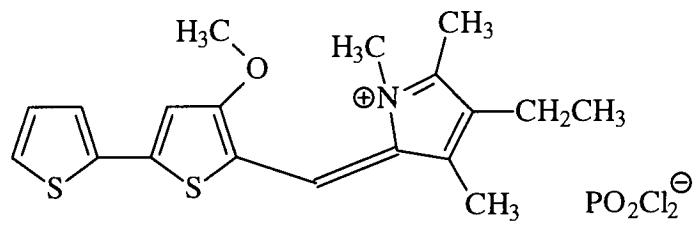
This compound was then coupled to the bithiophene intermediate to produce the analogue **304**. Again, this was isolated as a thick, purple oil in an excellent yield of 97%, after a 15 min reaction. The compound was identified by spectroscopic methods; the two key signals in the ^{1}H NMR spectrum, a singlet due to the methine proton at 8.40 p.p.m. and a broad peak due to the NH proton at 13.6 p.p.m., helped confirm the identity of the product **304**.

The NH proton has been shown by X-ray crystallography (of analogue **85a**[87]) to play an important role in the geometry of the compound, by forming a 7-membered hydrogen bonded ring with the oxygen atom of the methoxy group on Ring B. Consequently it was of interest, in terms of biological activity and the structure-activity relationships being researched by Professor Okhuma, as mentioned previously, to attempt to prepare prodigiosin analogues lacking this NH moiety.

The first analogue prepared contained an *N*-substituted Ring C pyrrole. 1,2,4-Trimethyl-3-ethylpyrrole **305** was prepared by *N*-methylating commercially available kryptopyrrole **289** in a 61% yield under standard pyrrole alkylation conditions,[171] using iodomethane and potassium hydroxide in dry dimethylsulfoxide.



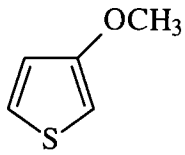
305



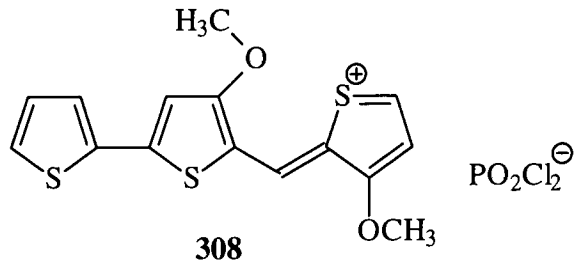
306

Coupling of the pyrrole to the bithiophene compound occurred in an excellent yield of 93%. The salt was again produced as a thick purple oil, and identified by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (of the cation).

The second analogue prepared contained only thiophene rings; 3-methoxythiophene **307** was chosen as the Ring C compound as the 2-position of this compound is activated by the electron-donating group.



307

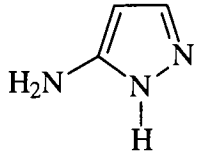


308

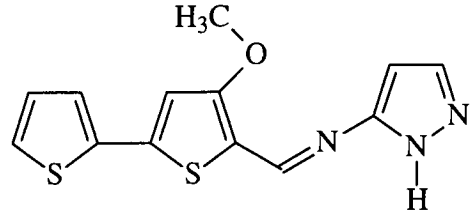
The prodigiosin analogue **308** was successfully isolated in a yield of 84%. However, the compound proved to be very insoluble and unstable, decomposing within 72 h of formation even when stored at -20 °C; consequently it was not possible to obtain a ^{13}C NMR spectrum. The compound's identity was confirmed on the basis of ^{1}H NMR spectroscopy and mass spectrometry of the cation.

A third reaction of the bithiophene intermediate with 2-methoxythiophene proved unsuccessful using these conditions, with unreacted starting material being quantitatively recovered.

In order to produce a prodigiosin analogue with further disruption to the hydrogen bonding regime, a pyrazole was reacted with the bithiophene A-B Ring system, namely 3-aminopyrazole **309**.



309



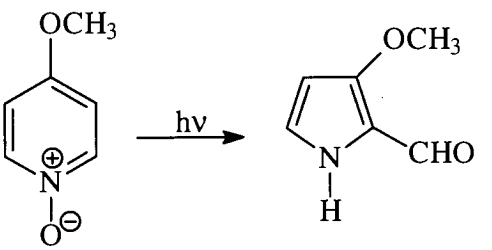
310

The analogue **310** was obtained by heating the reaction mixture under reflux using propan-2-ol as solvent and a reflux time of 24 h; the condensation proceeded as expected and the intense yellow-coloured solid product was obtained in a yield of 63%. The product identity was again confirmed by spectroscopic methods.

Repeating this reaction with different Ring C compounds, namely 2-aminopyridine and 2-aminopyridinium picrate failed to give any of the desired products, even after extended reflux times.

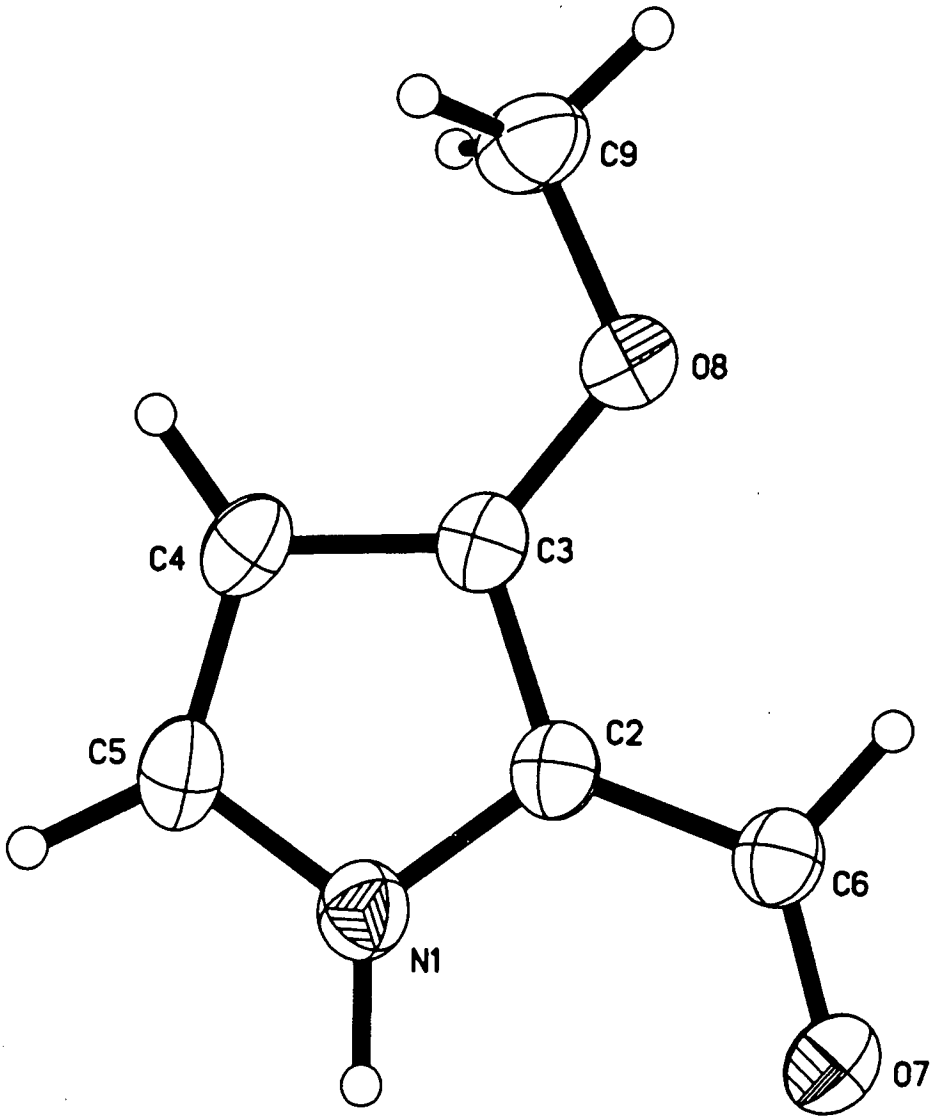
In order to further structure-activity relationship information, a final analogue of prodigiosin was prepared that lacked Ring A, i.e. a B-C Ring system.

The B Ring compound **311**, was prepared from 4-methoxypyridine-*N*-oxide **312** *via* photolysis,[152] as described earlier. Again, the photolysis yield was poor, at 11%, but this was not uncommon for this type of reaction.



312 **311**

Due to the interesting combination of electron-donating and electron-withdrawing groups on the pyrrole ring a crystal structure[172] was obtained of compound **311** and this is shown in **Scheme 81**, with associated bond lengths, bond angles and torsion angles in **Tables 39**, **40** and **41**.



Scheme 81

Table 39 - Bond Lengths (Å)

N(1)-C(5)	1.352(3)
N(1)-C(2)	1.383(3)
N(1)-H(1)	0.99(2)
C(2)-C(3)	1.393(3)
C(2)-C(6)	1.423(3)
C(3)-O(8)	1.348(3)
C(4)-C(5)	1.371(4)
C(4)-H(4)	0.94(2)
C(5)-H(5)	1.00(3)
C(6)-O(7)	1.223(3)
C(6)-H(6)	0.99(2)
O(8)-C(9)	1.425(3)
C(9)-H(91)	0.97(3)
C(9)-H(92)	1.03(3)
C(9)-H(93)	0.98(3)

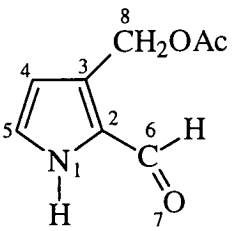
Table 40 - Bond Angles (degrees)

C(5)-N(1)-C(2)	108.7(2)
C(5)-N(1)-H(1)	125.4(16)
C(2)-N(1)-H(1)	125.9(16)
N(1)-C(2)-C(3)	106.8(2)
N(1)-C(2)-C(6)	123.7(2)
C(3)-C(2)-C(6)	129.4(2)
O(8)-C(3)-C(2)	122.2(2)
O(8)-C(3)-C(4)	129.7(2)
C(2)-C(3)-C(4)	108.1(2)
C(5)-C(4)-C(3)	106.5(2)
C(5)-C(4)-H(4)	128.4(14)
C(3)-C(4)-H(4)	125.1(14)
N(1)-C(5)-C(4)	109.9(2)
N(1)-C(5)-H(5)	118.6(14)
C(4)-C(5)-H(5)	131.5(13)
O(7)-C(6)-C(2)	125.8(2)
O(7)-C(6)-H(6)	121.9(13)
C(2)-C(6)-H(6)	112.2(13)
C(3)-O(8)-C(9)	116.1(2)
O(8)-C(9)-H(91)	109.3(15)
O(8)-C(9)-H(92)	110.4(14)
H(91)-C(9)-H(92)	112(2)
O(8)-C(9)-H(93)	110.8(16)
H(91)-C(9)-H(93)	104(2)
H(92)-C(9)-H(93)	110(2)

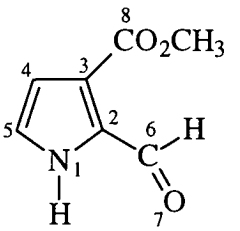
Table 41 - Torsion Angles (degrees)

C(5)-N(1)-C(2)-C(2)	0.3(3)
C(5)-N(1)-C(2)-C(6)	-176.7(2)
C(2)-N(1)-C(5)-C(4)	-0.7(3)
N(1)-C(2)-C(3)-O(8)	179.9(2)
N(1)-C(2)-C(3)-C(4)	0.3(3)
C(6)-C(2)-C(3)-O(8)	-3.4(4)
C(6)-C(2)-C(3)-C(4)	177.0(2)
N(1)-C(2)-C(6)-O(7)	-2.1(4)
C(3)-C(2)-C(6)-O(7)	-178.4(2)
C(2)-C(3)-O(8)-C(9)	176.6(2)
C(4)-C(3)-O(8)-C(9)	-3.9(3)
O(8)-C(3)-C(4)-C(5)	179.9(2)
C(2)-C(3)-C(4)-C(5)	-0.7(3)
C(3)-C(4)-C(5)-N(1)	0.9(3)

The crystal structure of the pyrrole was analysed in conjunction with other crystal structures obtained for the pyrroles **313**[173] (reported previously) and a new compound, **314**.[172]



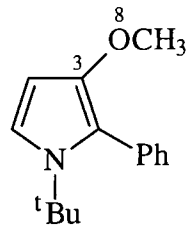
313



314

The three different substituents at the 3-position range from electron-donating (**311**), through a substituent which has minimal electronic effects on the ring (**313**) to a strongly electron-withdrawing group (**314**). The electronic properties of substituents have often been found to influence the geometry of unsaturated systems[137] and this aspect was of interest when comparing the three formylpyrroles.

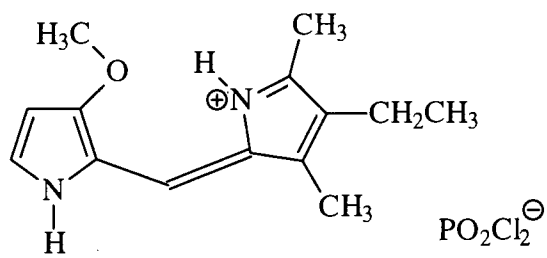
Very surprisingly, examination of the bond lengths in these three compounds showed there to be no significant differences between corresponding bond lengths in the pyrrole rings, with the exception of the N(1)-C(2) bond. This bond is affected by the degree of delocalisation of the nitrogen atom's lone pair into the substituent; consequently the N(1)-C(2) bond length is shortest in **314** [1.365(3) Å], intermediate in **313** [1.377(4) Å] and longest in **311** [1.383(3) Å]. There is a corresponding decrease in the C(2)-C(6) bond length, reflecting the delocalisation of the C(3) substituent lone pair into the aldehyde moiety; CO_2CH_3 [1.444(3) Å] > CH_2OAc [1.433(4) Å] > OCH_3 [1.423(3) Å]. In accordance with this, the C(3)-O(8) bond in compound **311** [1.348(3) Å] is significantly shortened, when compared with another methoxypyrrole compound, for example **314**, whose C(3)-O(8) bond length is 1.383(4) Å.[102]



315

The exocyclic bond angle C(2)-C(3)-C(8)/O(8) is affected by the bulk of the C(3) substituent and increases in the order OCH_3 [122.2(2)°] < CO_2CH_3 [125.2(2)°] < CH_2OAc [127.1(3)°]. There were no significant differences in the endocyclic bond angles in the three compounds. In compounds **311** and **314** intermolecular hydrogen bonding occurs, and packing in the structures is characterised by the formation of hydrogen bonded dimers *via* N-H···O=C interactions.

The methoxypyrrole **311** was then coupled successfully to commercially available kryptopyrrole to produce the prodigiosin analogue **316**.

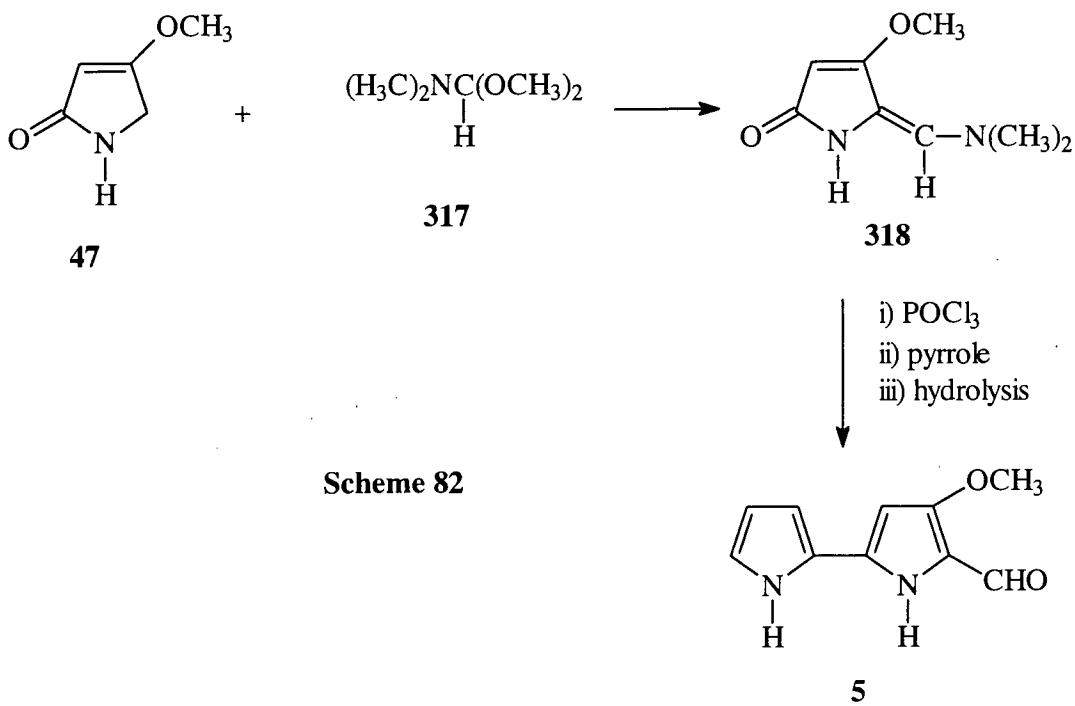


316

This compound was isolated as a thick, purple oil, in a good yield of 86%. The free base was also produced (by basic extraction of the hydrodichlorophosphate salt) in a good yield of 80%. Again, both compounds were characterised by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

A different approach into the prodigiosin ring system was suggested by a recent publication[63] of the synthesis of undecylprodigiosin (see Introduction, page 27) and an earlier publication by Bordner and Rapoport,[174] both utilising pyrrolinone chemistry.

A possible route into the key methoxybipyrrole carboxaldehyde **5** was designed which is illustrated in **Scheme 82**.



Scheme 82

The 2-substituted pyrrolone **318**, with its active methylene group now masked, was successfully prepared from the commercially available pyrrolinone **47** and dimethylformamide dimethylacetal **317**. However, preliminary work using a straightforward application of literature conditions[174] to produce the carboxaldehyde **5** was unsuccessful, with much insoluble black polymer always being produced. Due to these poor results this line of work was not continued; future work in this area

could include work at low temperature, milder conditions and further modifications of the pyrrolinone in an attempt to control this highly reactive reaction.

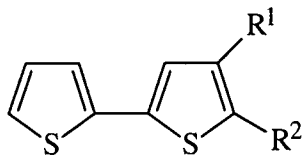
Except for the unstable compound **308**, with a thiophene Ring C, all of the prodigiosin analogues prepared (including the bithiophene A-B Ring system **290** and its precursors **293** and **294**) were tested for their inhibitory effects on the proton pump activity of lysosomal $H^{\oplus}$-ATPase. This work was carried out by Professor Okhuma at Kanazawa University, Japan and the results obtained are shown in **Table 42**, along with those for authentic samples of prodigiosin **1**, undecylprodigiosin **2** and metacycloprodigiosin **3**. It should be noted that the figures quoted in the table are minimum values for the compounds; retesting is currently underway with new samples to ensure compounds had not decomposed prior to testing. Consequently IC_{50} values may improve for some analogues.

Table 42

Compound	Inhibition of proton pump activity* IC_{50} (nM)
1	0.9
2	1.8
3	0.7
85a	150
303	8000
304	2000
306	200
310	100,000
316	20
290	no inhibition upto 1000
293	no inhibition upto 1000
294	no inhibition upto 1000

*We are most grateful to Professor Okhuma for supplying this data prior to publication

Preliminary analysis of the data shown in the table reveals many interesting features in terms of structure-activity relationships. As was expected, the bithiophene A-B Ring systems **290**, **293** and **294** show no inhibitory effects up to concentrations of 1000 nM, indicating the importance of Ring C in the activity of these types of compounds.



293 $R^1 = OH$ $R^2 = H$
294 $R^1 = OCH_3$ $R^2 = H$
290 $R^1 = OCH_3$ $R^2 = CHO$

The IC_{50} value for compound **310** (incorporating 3-aminopyrazole) of 100,000 nM also indicated the importance of Ring C and the hydrogen bonding regime, which is disrupted in this compound by extension of the length of the "bridge" between the B Ring and the neutral C Ring.

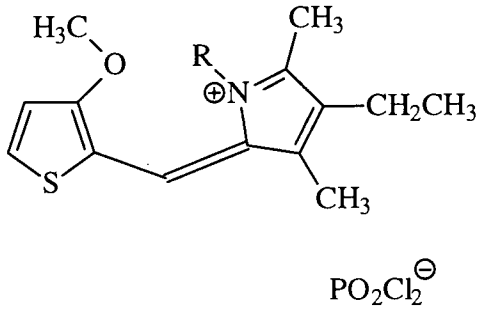
Very surprisingly, relatively poor IC_{50} results were obtained for compounds **303** and **304**, which both contain Ring C pyrroles found in naturally occurring prodigiosin compounds, with values of 8000 nM and 2000 nM respectively. Replacement of the Ring C with the commercially available kryptopyrrole (compound **85a**) significantly improved the activity, giving an IC_{50} value of just 150 nM, a very promising figure.

In light of previous results, disrupting the hydrogen bonding regime (by introducing a substituent on the nitrogen atom of Ring C) would have been expected to result in poor activity; however, methylation at this site (as in compound **306**) had little effect on the IC_{50} value, which rose by only 50 nM to 200 nM.

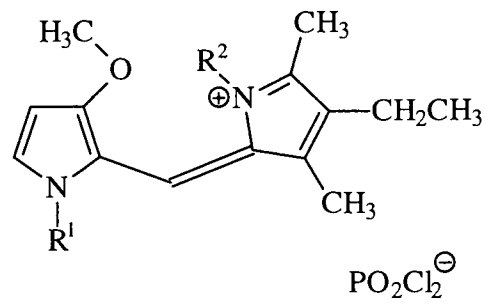
The most promising result of all was that obtained with compound **316**, which gave an IC_{50} of only 20 nM. In this analogue, Ring B is a pyrrole ring, as found in the

authentic prodigiosin family, which may be having a significant effect on the activity. The lack of a Ring A in this compound appears to have little effect, which is again a surprising result.

This set of preliminary work is very encouraging, and has provided valuable information for the structure-activity relationships being developed in Japan. These results have also indicated avenues for future work, such as preparation of the compounds shown in **Scheme 83**, which are further adaptations of compound **316**, as well as those that incorporate different Ring C moieties into the compound, such as 2-methyl-3-pentylpyrrole which is the Ring C of prodigiosin itself.



(**a**) R = H
(**b**) R = CH_3



(**a**) R^1 = H, R^2 = CH_3
(**b**) R^1 = CH_3, R^2 = CH_3
(**c**) R^1 = CH_3, R^2 = H

Scheme 83

EXPERIMENTAL

ABBREVIATIONS

NMR	nuclear magnetic resonance
δ_H, δ_C	chemical shift
p.p.m.	parts per million
FAB	fast atom bombardment mass spectrometry
DMSO	dimethyl sulfoxide
FVP	flash vacuum pyrolysis
mol	moles
mmol	millimoles
M	molarity
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
q	quartet (^{1}H spectra) / quaternary (^{13}C spectra)
m	multiplet
br	broad
J	coupling constant
mp	melting point
bp	boiling point
m/z	mass to charge ratio
M^+	mass of molecular ion
h	hours
min	minutes
atm	atmospheres
p.s.i.	pounds per square inch

1. INSTRUMENTATION AND GENERAL TECHNIQUES

(a) Nuclear Magnetic Resonance Spectroscopy

^1H NMR spectra were recorded on Bruker WH360 (360 MHz), Bruker AC250 (250 MHz), Bruker AC200 (200 MHz) and Varian Gemini 200 (200 MHz) spectrometers. ^{13}C NMR spectra were obtained on Bruker WH360 (90 MHz), AC250 (63 MHz) and AC200 (50 MHz) instruments.

The Bruker WH360 was operated by Dr D. Reed, the Bruker AC250 by Mr. J.R.A. Millar, the Bruker AC200 by Mr W.G. Kerr and Dr. H. McNab, and the Varian Gemini 200 by Miss K. Withell.

Spectra were recorded in [^2H] chloroform, unless otherwise stated. Chemical shifts (δ_H and δ_C) are quoted in p.p.m., relative to tetramethylsilane, and all coupling constants are given in Hertz (Hz).

(b) Mass Spectrometry

Low resolution electron impact mass spectra were recorded by Miss E. Stevenson on A.E.I. MS902 and Finnigan 4500 instruments and by Mr H.G. McKenzie on a Finnigan 4600 instrument. High resolution and FAB mass spectra were obtained on a Kratos MS50 TC instrument operated by Mr A.T. Taylor.

All spectra were obtained by electron impact instruments unless otherwise stated.

(c) Elemental Analysis

Microanalyses were carried out on a Perkin Elmer 240 CHN Elemental Analyser by Mrs. L. Eades, Mr S. Franklin and Mr D. Glass.

(d) Structure Determination

X-ray crystal structure data were obtained and solved by Dr. A.J. Blake, Dr. R.O. Gould and Dr. S. Parsons on a Stoë STADI-4 four circle diffractometer, with graphite monochromator.

(e) Chromatography

Thin-layer chromatography was carried out on precoated aluminium sheets (0.2 mm silica gel, Merck, grade 60) impregnated with an ultra violet indicator.

Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å) by the method of Harwood.[175] The crude materials were generally preabsorbed onto silica gel and then loaded onto the column. Ethyl acetate and *n*-hexane were frequently used as the solvent system with 10% increments in the polar component every two of three fractions.

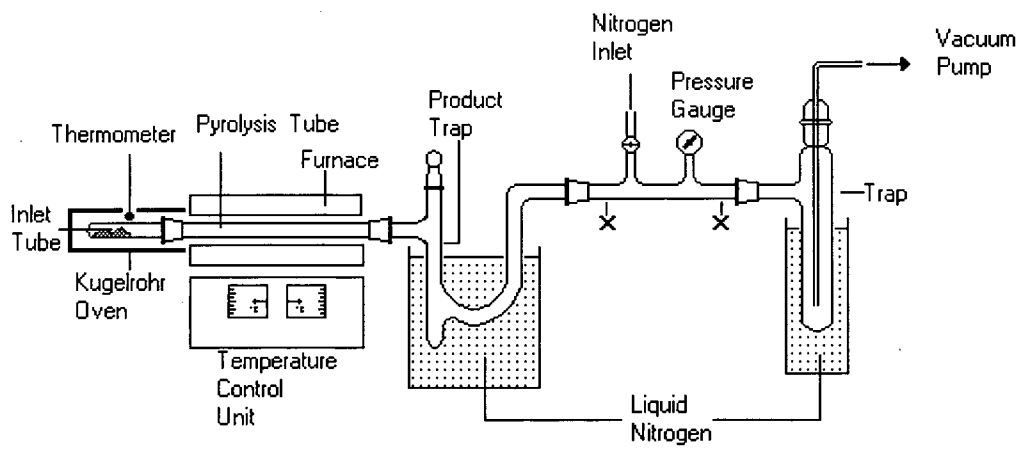
(f) Solvents

Tetrahydrofuran and diethyl ether were both dried by distillation from sodium using benzophenone as an indicator. Other commercially available solvents were dried over molecular sieves or used without further purification

2. FLASH VACUUM PYROLYSIS

The technique of FVP involves the exposure of gaseous molecules to high temperatures for very short periods of time, typically 10^{-2}-10^{-3} seconds. The apparatus used in such experiments is illustrated in **Scheme 12**, and is based on the design of W.D. Crow of the Australian National University. In principle the substrate is distilled or sublimed through an electrically heated tube which is connected to a cold trap and vacuum line.

Volatilisation of the substrate at temperatures lower than 300 °C was achieved by a glass Büchi drying oven. The volatilised substrate was then drawn through a silica tube (30 x 2.5 cm) which was heated by a Stanton Redcroft laboratory tube furnace. The temperature within the furnace was monitored and controlled by a platinum/platinum 13% rhodium thermocouple. On exiting the furnace the product(s) were collected in a trap cooled by a liquid nitrogen bath. For a small scale pyrolyses (up to 2 g of starting material) the 'U-shaped' trap (**Scheme 12**) suffices; for larger scale pyrolyses this trap can be replaced with a larger 'finger trap' in order to avoid blockages. The vacuum was maintained, typically at 10^{-2}-10^{-3} Torr by an Edwards Model ED100 high capacity oil pump.



Scheme 12

The product(s) formed were normally sufficiently pure that they could be either scraped from the trap for analysis or washed through with a suitable solvent. For small scale pyrolyses (50-100 mg) the solvent of choice was frequently [^{2}H]chloroform enabling immediate examination by ^{1}H and ^{13}C NMR spectroscopy.

Standard pyrolysis parameters used throughout this section are furnace temperature, inlet temperature, pressure, sublimation time and mass of substrate.

A. THE *N*-BENZYL PROTECTING GROUP

1. Preparation of 1-Benzyl-3-methoxy-2-phenylpyrrole

(a) Preparation of 5-*N*,*N*-dibenzylaminomethylidene Meldrum's acid[90]

A solution of 5-methoxymethylidene Meldrum's acid (3.72 g, 20 mmol) and dibenzylamine (3.94 g, 20 mmol) in acetonitrile (50 cm^3) was stirred at room temperature for 30 min. The solvent was then removed under reduced pressure and the crude orange solid recrystallised to give the desired product **116** (6.56 g, 93%), mp 151-152 °C (from ethanol) (lit.,[90] 152°C); δ_H 8.21 (1H, s), 7.26-6.91 (10H, m), 4.85 (2H, s). 4.53 (2H, s) and 1.27 (6H, s).

(b) Preparation of 1-benzyl-3-hydroxy-2-phenylpyrrole

5-*N*,*N*-Dibenzylaminomethylidene Meldrum's acid was sublimed at low pressure through the furnace tube (600 °C, 195 °C, 0.01 Torr, 6 h, 3.51 g) and the product was collected in a trap cooled in liquid nitrogen. Upon completion of the pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The red/brown oil produced was washed from the trap with solvent and after the solvent had been removed under reduced pressure, the crude pyrolysate was purified by Kugelrohr distillation to give the desired product **118** which existed as a mixture of tautomers in deuteriated chloroform, (1.57 g, 63%), bp 180 °C (0.3 Torr) [lit.,[90] 180-182 °C (0.3 Torr)]; δ_H (keto tautomer) 8.04 (1H, d, ^3J 3.3), 7.48-7.02 (10H, m), 5.17 (1H, d, ^3J 3.3), 4.52 (1H, d, ^2J 14.6), 4.39 (1H, s) and 4.03 (1H, d, ^2J 14.6); δ_H (enol tautomer) 7.48-7.02 (10H, m), 6.49 (1H, d, ^3J 3.3), 5.95 (1H, d, ^3J 3.3) and 5.01 (2H, s).

(c) Preparation of 1-benzyl-3-methoxy-2-phenylpyrrole[102]

To a stirred suspension of sodium hydride (80% dispersion in oil, 0.907 g, ~19 mmol, washed three times with *n*-hexane and dried at 0.1 Torr) in dimethylimidazolidinone (40 cm^3) was added a solution of 1-benzyl-3-hydroxy-2-phenylpyrrole (1.569 g, 6.3 mmol) in dimethylimidazolidinone (10 cm^3) under a stream of nitrogen. A solution of methyl *p*-toluenesulfonate (1.173 g, 6.3 mmol) in dimethylimidazolidinone (20 cm^3) was then added dropwise and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then quenched in ethanol/water (100 cm^3, 1:1) and extracted with ether (3 x 100 cm^3). The combined organic layers were back-extracted with water (5 x 150 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the desired product **119** (0.68 g, 41%), mp 32-34°C (lit.,[102] 33-34°C); δ_H 7.37-6.99 (10H, m), 6.55 (1H, d, ^3J 3.3), 6.08 (1H, d, ^3J 3.3), 5.06 (2H, s) and 3.78 (3H, s); δ_C 145.24 (q), 138.54 (q), 130.99 (q), 129.37, 128.42, 128.14, 127.13, 126.14, 126.32, 118.94, 118.35 (q), 96.15, 58.37 and 50.85; *m/z* 263 (M^+, 62%), 248 (54), 220 (29), 196 (11), 182 (22), 172 (42), 157 (21), 117 (16), 115 (17), 103 (45), 92 (49), 91 (100), 84 (37) and 65 (60).

2. Attempted Removal of the *N*-Benzyl Protecting Group

Method

To a suspension of catalyst (10 mg) in the appropriate solvent (10 cm^3) was carefully added a solution of 1-benzyl-3-methoxy-2-phenylpyrrole in the same solvent (10 cm^3). The mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and room temperature for the time quoted. The mixture was then filtered through a celite pad and the solvent was removed from the filtrate (except in the case of glacial acetic acid where a basic, extractive work-up was used), leaving a residue which was examined by ^1H NMR spectroscopy. The following combinations of catalyst, solvent and reaction time were tried:

(a) 5% Pd-C / Ethanol / 4 h

(b) 5% Pd-C / Glacial acetic acid / 4 h

(c) 20% $Pd(OH)_2$ / Methanol / 6 h

(d) 20% $Pd(OH)_2$ / Glacial acetic acid / 4 h

(e) 20% $Pd(OH)_2$ / Glacial acetic acid / 24 h

None of the above combinations succeeded in removing the benzyl group from the nitrogen atom, and unreacted starting material was always recovered.

B. THE *N*-SILYL PROTECTING GROUP

1. Protection of Primary Amines

Method[113,114]

To a stirred solution of the appropriate amine (freshly distilled and dried over potassium hydroxide pellets, 2 mmol) in dry acetonitrile (6 cm^3), under nitrogen, was added triethylamine (0.304 g, 3.5 mmol) and *t*-butyldiphenylsilyl chloride (0.550 g, 2 mmol). The mixture was stirred at room temperature for the time quoted below and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of 4:1 hexane/ethyl acetate (25 cm^3) and washed with aqueous sodium hydrogen carbonate (1M, 3 x 25 cm^3). The combined aqueous washings were back extracted with 4:1 hexane/ethyl acetate and the combined organic layers were dried ($MgSO_4$). The solvent was then removed under reduced pressure to give the desired product as a creamy opaque oil. The following compounds were prepared in this manner. The amine used and reaction time are given for each example in brackets.

***N*-(*t*-Butyldiphenylsilyl)cyclohexylamine**[113] **127** (cyclohexylamine, 3 h), (76%), bp 190 °C (1.1 Torr); δ_H 7.75-7.69 (4H, m), 7.41-7.30 (6H, m), 2.57 (1H, br), 1.88-0.91 (11H, m) and 1.06 (9H, s); δ_C 136.11 (q), 135.92, 128.83, 127.17, 50.65, 38.44, 27.51, 25.68, 25.41 and 18.32 (q).

***N*-(*t*-Butyldiphenylsilyl)benzylamine 130a** (benzylamine, 24 h), (82%), bp 170 °C (0.3 Torr), (Found: M^+, 345.1914. $C_{23}H_{27}NSi$ requires *M*, 345.1913); δ_H 7.78-7.71 (5H, m), 7.42-7.31 (10H, m), 3.96 (2H, s), 1.25 (1H, br) and 1.06 (9H, s); δ_C 143.60 (q), 135.76, 135.02 (q), 129.11, 128.19, 127.47, 126.90, 126.39, 46.58, 27.43 and 18.55 (q); *m/z* 345 (M^+, 1%), 288 (100), 271 (15), 259 (54), 210 (19), 199 (33), 183 (34), 181 (21) and 105 (15).

***N*-(*t*-Butyldiphenylsilyl)-1-phenylethylamine**[114] **130b** (α-methylbenzylamine, 24 h), (75%), bp 165 °C (0.1 Torr) [lit.,[114] 180 °C (0.5 Torr)]; δ_H 7.68-7.62 (3H, m), 7.48-7.43 (2H, m), 7.34-7.03 (10H, m), 3.85 (1H, br m), 1.58 (1H, br), 1.23 (3H, d, ^3J 6.6) and 0.93 (9H, s); δ_C 148.83 (q), 136.02, 135.89, 135.74 (q), 134.83 (q), 129.01, 128.87, 128.00, 127.32, 127.11, 126.39, 125.98, 51.80, 28.07, 27.45 and 18.48 (q); *m/z* 302 (M^+ - C_4H_9, 100%), 259 (41), 199 (39), 183 (19), 181 (14), 105 (17) and 77 (8).

Note

In all of the reactions, the use of "wet" acetonitrile, or "wet" amines resulted in a dramatic fall in yield of the desired product and the production of *t*-butyldiphenylsilanol **128** mp 61-62 °C (from toluene) (lit.,[176] 62-64 °C); δ_H 7.75-7.69 (4H, m), 7.45-7.34 (6H, m), 2.25 (1H, s) and 1.08 (9H, s); δ_C 135.06 (q), 134.70, 129.48, 127.57, 26.44 and 18.85 (q); *m/z* 256 (M^+, 25%), 201 (78), 200 (93), 199 (62), 198 (83), 181 (75), 152 (17), 137 (30), 121 (52), 78 (57) and 77 (100).

2. Reactions of *N*-Silyl Protected Amines With 5-Methoxymethylidene Meldrum's Acid

(a) Method 1

The amine (0.5 mmol) was dissolved in dry acetonitrile (10 cm^3) and 5-methoxymethylidene Meldrum's acid (0.093 g, 0.5 mmol) was added with stirring. The mixture was stirred at room temperature for 5 min and the solvent was removed under reduced pressure to give a yellow solid. Examination of the crude product by ^1H NMR spectroscopy showed the product was not the desired *N*-protected aminomethylidene Meldrum's acid derivative, but that it was a mixture of *t*-butyldiphenylsilanol and the deprotected aminomethylidene Meldrum's acid compound. The following aminomethylidene Meldrum's acid derivatives were isolated. The amine used for each example is given in brackets.

2,2-Dimethyl-5-(*N*-benzylaminomethylidene)-1,3-dioxane-4,6-dione 131 [*N*-(*t*-butyldiphenylsilyl)benzylamine] (80%), mp 166-167 °C (from ethanol) (Found: C, 63.9; H, 5.8; N, 5.35. $C_{14}H_{15}NO_4$ requires C, 64.35; H, 5.8; N, 5.35%); δ_H 9.75 (1H, br), 8.18 (1H, d, ^3J 14.8), 7.36-7.19 (5H, m), 4.55 (2H, d, ^3J 6.0) and 1.61 (6H, s); δ_C 165.16 (q), 163.58 (q), 134.81 (q), 128.79, 128.26, 127.38, 104.25 (q), 84.50 (q), 53.59 and 26.50; *m/z* 261 (M^+, 18%), 204 (16), 203 (21), 175 (10), 174 (30), 159 (18), 130 (45), 97 (12), 91 (100), 77 (18) and 69 (30).

2,2-Dimethyl-5-(*N*-cyclohexylaminomethylidene)-1,3-dioxane-4,6-dione 100 [*N*-(*t*-butyldiphenylsilyl)cyclohexylamine] (55%), mp 150-151 °C (from ethanol) (lit.,[97] 149-151 °C); δ_H 9.48 (1H, br), 8.16 (1H, d, ^3J 14.8), 3.27 (1H, br), 1.71 (6H, s) and 2.08-1.02 (10H, m).

2,2-Dimethyl-5-[*N*-(α-methylbenzyl)aminomethylidene]-1,3-dioxane-4,6-dione

132 [*N*-(*t*-butyldiphenylsilyl)-1-phenylethylamine] (81%), mp 113-115 °C (from ethanol), (lit.,[97] 113-116 °C); δ_H 9.76 (1H, br), 8.16 (1H, d, ^3J 14.4), 7.47-7.23 (5H, m), 4.70 (1H, m), 1.68 (6H, s) and 1.66 (3H, d, ^3J 6.9).

(b) Method 2[90]

N-(*t*-Butyldiphenylsilyl)-1-phenylethylamine (0.179 g, 0.5 mmol) was dissolved in cyclohexane (10 cm^3) and 5-methoxymethylidene Meldrum's acid (0.093 g, 0.5 mmol) was added with stirring. The mixture was heated under reflux for 24 h and the solvent was removed under reduced pressure to give a yellow solid. Examination of the crude product by ^1H NMR spectroscopy showed the product was not the desired *N*-protected aminomethylidene Meldrum's acid derivative, but that it was unreacted starting material.

C. THE *N*-AMINO PROTECTING GROUP

1. Preparation of Hydrazines

2-Benzyl-1,1-dimethylhydrazine[115]

(a) To a stirred, ice-cooled solution of 1,1-dimethylhydrazine (18.62 g, 0.31 mol) in acetonitrile (30 cm^3) was added benzyl chloride (39.24 g, 0.31 mol) dropwise over a period of 45 min. The mixture was then heated under reflux for 3 h, and the solvent was removed under reduced pressure to give 1-benzyl-1,1-dimethylhydrazinium chloride **135** (41.25 g, 71%); δ_H 7.78-7.38 (5H, m), 6.90 (2H, br s), 5.21 (2H, s) and 3.59 (6H, s).

(b) 1-Benzyl-1,1-dimethylhydrazinium chloride (3.0 g, 16 mmol) and crushed potassium hydroxide pellets (2.25 g, 40 mmol) were well mixed, and then distilled by Kugelrohr (200-300 °C, 30 Torr) to give the title compound **136** (2.00 g, 83%), bp 50 °C (1.0 Torr) (lit.,[115] 206-208 °C); δ_H 7.40-7.17 (5H, m), 3.94 (2H, s) and 2.49 (6H, s); δ_C 138.85 (q), 128.16 (4 x C), 126.84, 52.78 and 47.53.

2. Preparation of Aminomethylidene Meldrum's Acid Derivatives

Method

To a solution of 2,2-dimethyl-5-methoxymethylidene-1,3-dioxane-4,6-dione[94] (5-methoxymethylidene Meldrum's acid) (1.86 g, 10 mmol) in acetonitrile (50 cm^3) was added the appropriate hydrazine (10 mmol) and the mixture was stirred at room temperature for 10 min. The solvent was then removed under reduced pressure to give the crude product which was recrystallised. The following aminomethylidene derivatives were prepared. The hydrazine used for each example is given in brackets.

2,2-Dimethyl-5-[(*N*-benzyl-*N*-dimethylamino)aminomethylidene]-1,3-dioxane-4,6-dione 137 (1-benzyl-2,2-dimethylhydrazine), (44%), mp 111-113 °C (from cyclohexane), (Found: C, 63.2; H, 6.3; N, 9.0. $C_{16}H_{20}N_2O_4$ requires C, 63.15; H, 6.6; N, 9.2%); δ_H 8.45 (1H, s), 7.30-7.13 (5H, m), 5.16 (2H, s), 2.70 (6H, s) and 1.27 (6H, s); δ_C [2 quaternaries missing], 156.61, 133.92 (q), 128.51, 128.20, 127.68, 102.72 (q), 85.14 (q), 52.08, 44.96 and 25.85; *m/z* 304 (M^+, 3%), 247 (34), 246 (30), 203 (16), 155 (50), 139 (17), 130 (15) and 91 (100).

2,2-Dimethyl-5-[(*N*-dimethylamino)aminomethylidene]-1,3-dioxane-4,6-dione 144 (1,1-dimethylhydrazine), (79%), mp 188-190 °C (from ethanol), (Found: C, 50.5; H, 6.6; N, 13.15. $C_9H_{14}N_2O_4$ requires C, 50.45; H, 6.6; N, 13.1%); δ_H 9.76 (1H, br d), 8.19 (1H, d, ^3J 11.7), 2.55 (6H, s), and 1.52 (6H, s); δ_C 164.49 (q), 162.99 (q), 157.56, 104.00 (q), 82.12 (q), 47.79 and 26.33; *m/z* 214 (M^+, 2%), 194 (16), 157 (20), 156 (100), 83 (10) and 70 (58).

3. Pyrolyses of Aminomethylidene Meldrum's Acid Derivatives

Method

The appropriate derivative was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The entire pyrolysate was then dissolved in solvent to enable removal from the trap. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets.

2,2-Dimethyl-5-[(*N*-benzyl-*N*-dimethylamino)aminomethylidene]-1,3-dioxane-4,6-dione [475 °C, 270 °C, 0.01 Torr, 20 min, 0.609 g]

The pyrolysis generated black, polymeric material which proved to be insoluble. The minor, soluble product(s) were removed from the trap with dichloromethane and subjected to dry flash chromatography, eluting with a mixture of *n*-hexane and ethyl acetate. The only identifiable product obtained was bibenzyl **139** [70 mg, 38% (based on 1 mole of starting material giving 0.5 moles of product)], mp 46-49 °C (lit.,[177] 50-53 °C); δ_H 7.25 (10H, m) and 2.96 (4H, s); δ_C 141.65 (q), 128.32, 128.21, 125.79 and 37.82; *m/z* 182 (M^+, 15%), 167 (41), 159 (98), 113 (24), 97 (21), 91 (28), 85 (30), 83 (28), 71 (69) and 57 (100).

2,2-Dimethyl-5-[(*N*-dimethylamino)aminomethylidene]-1,3-dioxane-4,6-dione [600 °C, 210 °C, 0.01 Torr, 17 min, 1.00 g]

Pyrolysis again generated mainly insoluble, polymeric material. The very minor soluble portion of the product yielded no identifiable products, even after silica dry flash column chromatography.

D. THE AMIDE PROTECTING GROUP - PRIMARY AMIDES

1. Preparation of 5-(*N*-Amidomethylidene) Meldrum's Acid Derivatives[118]

(a) Method 1

To a stirred solution of 5-methoxymethylidene Meldrum's acid (1.86 g, 10 mmol) in acetonitrile (50 cm^3) was added the appropriate amide (10 mmol). The mixture was heated under reflux for the time quoted, and the solvent was removed under reduced pressure to give the crude product which was recrystallised. The following derivatives were prepared. The amide used and reflux time for each example are given in brackets.

2,2-Dimethyl-5-(*N*-formamidomethylidene)-1,3-dioxane-4,6-dione 153h (formamide, 96 h), (66%), mp 177-178 °C (from ethanol), (Found: C, 48.1; H, 4.85; N, 7.05. $C_8H_9NO_5$ requires C, 48.25; H, 4.55; N, 7.05%); δ_H ([$^2H_6$]DMSO) 11.46 (1H, br), 8.69 (1H, s), 8.56 (1H, s) and 1.68 (6H, s); δ_C ([$^2H_6$]DMSO) 163.57 (br), 162.31 (q), 162.15 (q), 149.35 (br), 105.31 (q), 93.75 (q) and 26.90; *m/z* 199 (M^+, 9%), 184 (17), 142 (26), 114 (20), 97 (25), 85 (14), 69 (45), 68 (39), 59 (66) and 43 (100).

2,2-Dimethyl-5-(*N*-acetamidomethylidene)-1,3-dioxane-4,6-dione 153a (acetamide, 24 h), (62%), mp 138-140 °C (from ethanol), (Found: C, 50.75; H, 5.35; N, 6.55. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.55); δ_H 10.94 (1H, br d), 8.70 (1H, d, ^3J 12.5), 2.27 (3H, s) and 1.64 (6H, s); δ_C 168.06 (q), 161.62 (q), 163.81 (q), 149.76, 105.35 (q), 93.13 (q), 26.98 and 23.48; *m/z* 213 (M^+, 26%), 198 (14), 171 (28), 160 (23), 156 (54), 155 (15), 114 (52), 111 (24), 57 (100), 51 (15) and 43 (100).

2,2-Dimethyl-5-(*N*-propionamidomethylidene)-1,3-dioxane-4,6-dione 153b (propionamide, 24 h), (58%), mp 141-142 °C (from ethanol), (Found: C, 52.8; H, 5.8; N, 6.05. $C_{10}H_{13}NO_5$ requires C, 52.85; H, 5.75; N, 6.15); δ_H 10.94 (1H, br d), 8.72 (1H, d, ^3J 12.8), 2.51 (2H, q, ^3J 7.4), 1.62 (6H, s) and 1.13 (3H, t, ^3J 7.4); δ_C 171.68 (q), 163.86 (q), 161.62 (q), 149.76, 105.24 (q), 92.90 (q), 29.70, 26.91 and 7.93; *m/z* 227 (M^+, 27%), 170 (37), 169 (41), 141 (18), 140 (28), 125 (17), 114 (54), 69 (20) and 57 (100).

2,2-Dimethyl-5-(*N-iso*-butyramidomethylidene)-1,3-dioxane-4,6-dione 153c (*iso*-butyramide, 48 h), (24%), mp 100-102 °C (from ethanol), (Found: C, 54.45; H, 5.9; N, 5.7. $C_{11}H_{15}NO_5$ requires C, 54.75; H, 6.25; N, 5.8); δ_H 11.12 (1H, br d), 8.80 (1H, d, ^3J 12.7), 2.66 (1H, septet, ^3J 6.9), 1.68 (6H, s) and 1.22 (6H, d, ^3J 6.9); δ_C 174.70 (q), 164.24 (q), 161.68 (q), 150.27, 105.45 (q), 93.29 (q), 35.77, 27.09 and 18.33; *m/z* 241 (M^+, 8%), 184 (9), 183 (8), 140 (18), 114 (20), 96 (10), 71 (45), 70 (20) and 43 (100).

2,2-Dimethyl-5-(*N*-trimethylacetamidomethylidene)-1,3-dioxane-4,6-dione 153d (trimethylacetamide, 72 h), (48%), mp 99-100 °C (from ethanol), (Found: C, 56.1; H, 7.05; N, 5.45. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5); δ_H 11.46 (1H, br d), 8.79 (1H, d, ^3J 12.6), 1.67 (6H, s) and 1.25 (9H, s); δ_C 176.27 (q), 164.48 (q), 161.62 (q), 150.71, 105.45 (q), 93.40 (q), 39.58 (q), 27.09 and 26.44; *m/z* 255 (M^+, 4%), 198 (13), 140 (12), 114 (8), 85 (11), 69 (10), 59 (11) and 57 (100).

2,2-Dimethyl-5-(*N*-benzamidomethylidene)-1,3-dioxane-4,6-dione 153e (benzamide, 48 h), (48%), mp 153-154 °C (from ethanol), (Found: C, 61.0; H, 4.85; N, 4.95. $C_{14}H_{13}NO_5$ requires C, 61.1; H, 4.75; N, 5.1%); δ_H 12.08 (1H, br d), 9.02 (1H, d, ^3J 12.4), 7.94 (2H, m), 7.66-7.51 (3H, m) and 1.72 (6H, s); δ_C 164.56 (q), 163.62 (q), 161.48 (q), 150.62, 134.15, 129.92 (q), 129.04, 128.01, 105.54 (q), 94.03 (q) and 27.06; *m/z* 275 (M^+, 3%), 218 (3), 173 (2), 106 (8), 105 (100), 77 (42) and 51 (15).

2,2-Dimethyl-5-[*N*-(thienyl-2-carboxamido)methylidene]-1,3-dioxane-4,6-dione

153f (thienyl-2-carboxamide, 96 h), (51%), mp 121-122 °C (from ethanol), (Found: C, 51.00; H, 4.00; N, 5.25. $C_{12}H_{11}NO_5S$ requires C, 51.5; H, 3.9; N, 5.0); δ_H ([$^2H_6$]DMSO) 11.71 (1H, br d), 8.65 (1H, d, ^3J 12.5), 8.16 (1H, dd, ^3J 4.8, ^4J 1.0), 7.92 (1H, dd, ^3J 3.8, ^4J 1.0), 7.33 (1H, dd, ^3J 4.8 and 3.8) and 1.71 (6H, s); δ_C ([$^2H_6$]DMSO) 163.84 (q), 161.74 (q), 158.54 (q), 149.59, 136.85, 134.79 (q), 133.22, 129.40, 105.73 (q), 93.97 (q) and 26.87; *m/z* 281 (M^+, 18%), 224 (10), 223 (18), 111 (100) and 83 (7).

(b) Method 2

To a stirred solution of 2,2-dimethyl-5-aminomethylidene-1,3-dioxane-4,6-dione[94] (1.71 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in acetonitrile (90 cm^3) was added the appropriate acid chloride (10 mmol) in acetonitrile (10 cm^3) dropwise over a period of 10 min. The mixture was heated under reflux for the time quoted and the solvent was then removed under reduced pressure. The crude product was redissolved in dichloromethane (50 cm^3) and the solution was washed with water (3 x 50 cm^3) and dilute, aqueous HCl (2M, 1 x 50 cm^3). The combined aqueous washings were back extracted with dichloromethane (2 x 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product which could be recrystallised. The following derivatives were prepared. The precursor acid chloride and reflux time for each example are given in brackets.

2,2-Dimethyl-5-(*N-iso*-butyramidomethylidene)-1,3-dioxane-4,6-dione 153c (*iso*-butyryl chloride, 2 h), (70%), mp 100-101 °C (from ethanol). Spectra obtained were identical to those reported for preparation of this compound by Method 1.

2,2-Dimethyl-5-[*N*-(2-carbomethoxyamidomethylidene]-1,3-dioxane-4,6-dione 153g (methyl oxalyl chloride, 8 h), (56%), mp 136-137 °C (from ethanol), (Found: C, 47.0; H, 4.7; N, 5.75. $C_{10}H_{11}NO_7$ requires C, 46.70; H, 4.3; N, 5.45); δ_H 12.08 (1H, br d), 8.70 (1H, d, ^3J 12.7), 3.98 (3H, s) and 1.71 (6H, s); δ_C 163.21 (q), 161.02 (q), 158.03 (q), 154.42 (q), 147.78, 105.98 (q), 97.32 (q), 54.47 and 27.30; *m/z* 257 (M^+, 3%), 200 (31), 198 (26), 140 (80), 114 (54), 96 (17), 70 (27) and 69 (100).

(c) Reaction of oxalyl chloride with 5-aminomethylidene Meldrum's acid[123]

(i) To a stirred solution of 5-aminomethylidene Meldrum's acid (1.71 g, 10 mmol) and triethylamine (2.04 g, 20 mmol) in acetonitrile (40 cm^3) was added a solution of oxalyl chloride (1.26 g, 10 mmol) in acetonitrile (10 cm^3) dropwise over a period of 10 min. The mixture was heated under reflux for 20 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (100 cm^3) and extracted with water (2 x 100 cm^3). A further portion of water (100 cm^3) was added and the gelatinous mixture was filtered through a celite pad. The organic layer was separated, washed with dilute hydrochloric acid (1M, 50 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude solid obtained was examined by ^1H NMR spectroscopy and shown to be *5-[N-(5-methylidene-2,2-dimethyl-4,6-dioxo-1,3-dioxane)aminomethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione* **164** (0.30 g, 18%), mp 228 °C (dec.) (from acetonitrile), (Found: C, 51.4; H, 5.05; N, 4.25. $C_{14}H_{15}NO_8$ requires C, 51.7; H, 4.65; N, 4.3); δ_H ([$^2H_6$]DMSO) 12.80 (1H, t, ^3J 12.6), 8.84 (2H, d, ^3J 12.6) and 1.70 (12H, s); δ_C ([$^2H_6$]DMSO) 162.65 (q), 161.34 (q), 156.33, 105.66 (q), 94.60 (q) and 26.95; *m/z* 325 (M^+, 19%), 268 (12), 267 (75), 210 (22), 209 (42), 181 (20), 165 (20), 153 (63), 137 (28), 121 (47) and 57 (100).

(ii) Repeating method (i), but omitting the addition of oxalyl chloride resulted in a quantitative recovery of unreacted starting material, so proving the involvement of the oxalyl chloride in the formation of the product obtained.

2. Attempted Formylation of 5-Aminomethylidene Meldrum's Acid

(a) Preparation of *N*-formylbenzotriazole[121]

To an ice-cooled mixture of benzotriazole (7.42 g, 0.063 mol) and formic acid (3.45 g, 0.075 mol) in anhydrous dichloromethane (125 cm^3) was added dropwise 1,3-dicyclohexylcarbodiimide (18.03 g, 0.088 mol). The resulting mixture was stirred at room temperature for 19 h and the precipitate formed during this time was removed by filtration. The solvent was removed from the filtrate under reduced pressure and the white, solid residue obtained was recrystallised to give the desired product **162** (6.55 g, 71%), mp 94-95 °C (from hexane) (lit.,[121] 94-96 °C); δ_H 9.81 (1H, s), 8.20-8.06 (2H, m) and 7.68-7.44 (2H, m).

(b) Reaction of *N*-formylbenzotriazole with 5-aminomethylidene Meldrum's acid

N-Formylbenzotriazole (0.74 g, 5 mmol) was dissolved in tetrahydrofuran (20 cm^3) and the mixture was heated under reflux. A solution of 5-aminomethylidene Meldrum's acid (0.9 g, 5.3 mmol) and triethylamine (2.0 g) in tetrahydrofuran (30 cm^3) was added dropwise and the mixture was heated under reflux for 4 days. The solvent was then removed from the red solution under reduced pressure and the residue was dissolved in dichloromethane (50 cm^3). The solution was washed with dilute sodium hydroxide (2M, 2 x 50 cm^3), water (1 x 50 cm^3) and dilute hydrochloric acid (2M, 1 x 50 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude solid examined by ^1H NMR spectroscopy, but was shown to be only unreacted 5-aminomethylidene Meldrum's acid.

(c) Acetic Formic Anhydride[122]

A mixture of acetic anhydride (6.2 cm^3) and formic acid (2.6 cm^3) was heated at ~55 °C for 1.5 h (condenser fitted with calcium chloride tube). The mixture was allowed to cool to room temperature and 5-aminomethylidene Meldrum's acid (5.13 g, 0.03 mol) was added portionwise over 15 min, taking care to maintain a reaction temperature of less than 39 °C. The mixture was then cooled to 30 °C and diethyl ether (15 cm^3) was added. The suspension was stirred at room temperature for 2 days and the solid formed was collected by filtration and washed with ether. ^1H NMR spectroscopy of the solid showed it to be unreacted starting material.

(d) *n*-Butyl Formate

5-Aminomethylidene Meldrum's acid (0.086 g, 0.5 mmol) was dissolved in *n*-butyl formate (25 cm^3) and heated under reflux for 2 h. The solvent was then removed under reduced pressure and the crude solid obtained examined by ^1H NMR spectroscopy, which showed it to be unreacted starting material.

3. Preparation of 2-Substituted-6*H*-1,3-Oxazin-6-ones[118]

Method

The appropriate 2,2-dimethyl-5-(*N*-amidomethylidene)-1,3-dioxane-4,6-dione was sublimed at low pressure through the furnace tube and the product was collected in a trap cooled in liquid nitrogen. Upon completion of the pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. Involatile solid products which condensed at the exit point of the furnace were scraped from the trap, whereas volatile solids and liquids were washed from the trap with solvent. After the solvent had been removed under reduced pressure, the crude pyrolysate was purified by either recrystallisation or Kugelrohr distillation. The following oxazinones were prepared by pyrolysis. The amidomethylidene Meldrum's acid precursor and pyrolysis conditions for each example are given in brackets.

6*H*-1,3-oxazin-6-one[128] **166h** [2,2-dimethyl-5-(*N*-formamido-), 450 °C; 250 °C, 0.02 Torr, 8 min, 0.2 g], (62%); δ_H 7.93 (1H, dd, ^4J 0.8, ^5J 1.7), 7.63 (1H, dd, ^3J 7.0, ^4J 0.8) and 6.28 (1H, dd, ^3J 7.0, ^5J 1.7); δ_C 156.72, 156.71 (q), 152.90 and 113.06.

2-Methyl-6*H*-1,3-oxazin-6-one 166a [2,2-dimethyl-5-(*N*-acetamido-), 500 °C, 150 °C, 0.01 Torr, 2 min, 0.5 g], (77%), bp 35-40 °C (0.15 Torr), (Found: M^+, 111.0321. $C_5H_5NO_2$ requires *M*, 111.0320); δ_H 7.55 (1H, d, ^3J 6.8), 6.09 (1H, d, ^3J 6.8) and 2.36 (3H, s); δ_C 168.31 (q), 158.39 (q), 153.83, 109.39 and 21.46; *m/z* 111 (M^+, 31%), 96 (19), 86 (38), 84 (48), 83 (32), 69 (17), 49 (29) and 43 (100).

2-Ethyl-6*H*-1,3-oxazin-6-one 166b [2,2-dimethyl-5-(*N*-propionamido-), 500 °C, 160 °C, 0.01 Torr, 37 min, 0.5 g], (62%), bp 40-45°C (0.2 Torr), (Found: M^+, 125.0473. $C_6H_7NO_2$ requires *M*, 125.0477); δ_H 7.53 (1H, d, ^3J 6.8), 6.03 (1H, d, ^3J 6.8), 2.54 (2H, q, ^3J 7.5) and 1.16 (3H, t, ^3J 7.5); δ_C 171.79 (q), 158.23 (q), 153.58, 109.23, 27.89 and 9.49; *m/z* 125 (M^+, 36%), 97 (11), 96 (75), 87 (12), 70 (26), 69 (11) and 57 (100).

2-*iso*-Propyl-6*H*-1,3-oxazin-6-one 166c [2,2-dimethyl-5-(*N*-isobutyramido-), 550 °C, 165 °C, 0.01 Torr, 31 min, 0.5 g], (68%), bp 40-45°C (0.4 Torr), (Found: M^+, 139.0638. $C_7H_9NO_2$ requires *M*, 139.0633); δ_H 7.58 (1H, d, ^3J 6.9), 6.06 (1H, d, ^3J 6.9), 2.79 (1H, septet, ^3J 7.0) and 2.22 (6H, d, ^3J 7.0); δ_C 174.80 (q), 158.53 (q), 153.82, 109.35, 34.03, 30.60 and 19.21; *m/z* 139 (M^+, 11%), 121 (9), 119 (10), 96 (47), 88 (22), 86 (74), 84 (100) and 71 (11).

2-*t*-Butyl-6*H*-1,3-oxazin-6-one 166d [2,2-dimethyl-5-(*N*-trimethylacetamido-), 550 °C, 135 °C, 0.02 Torr, 25 min, 0.5 g], (70%), bp 45-50°C (0.4 Torr), (Found: M^+, 153.0783. $C_8H_{11}NO_2$ requires *M*, 153.0790); δ_H 7.64 (1H, d, ^3J 6.8), 6.10 (1H, d, ^3J 6.8) and 1.32 (9H, s); δ_C 176.70 (q), 158.80 (q), 153.89, 109.31, 38.23 (q) and 27.45; *m/z* 153 (M^+, 15%), 138 (8), 125 (6), 110 (9), 96 (45), 84 (7), 70 (14), 69 (9) and 57 (100).

2-Phenyl-6*H*-1,3-oxazin-6-one 166e [2,2-dimethyl-5-(*N*-benzamido-), 550 °C, 150 °C, 0.01 Torr, 77 min, 0.5 g], (79%), mp 85-87 °C (from hexane/toluene) (lit.,[126] 85-87 °C); δ_H 8.19 (2H, m), 7.78 (1H, d, ^3J 6.7), 7.56-7.39 (3H, m) and 6.18 (1H, d, ^3J 6.7); δ_C 164.46 (q), 158.08 (q), 154.44, 133.24, 129.34 (q), 128.62, 128.31 and 109.28; *m/z* 173 (M^+, 10%), 146 (8), 106 (8), 105 (100), 77 (42) and 58 (25).

2-(2-Thienyl)-6*H*-1,3-oxazin-6-one 166f {2,2-dimethyl-5-[*N*-(thienyl-2-carboxamido)-], 550 °C, 180 °C, 0.01 Torr, 52 min, 0.5 g}, (72%), mp 109-110°C (from ethanol), (Found: C, 53.4; H, 2.85; N, 7.9. $C_8H_5NO_2S$ requires C, 53.6; H, 2.8; N, 7.8); δ_H 7.91 (1H, dd, ^3J 3.8, ^4J 1.2), 7.71 (1H, d, ^3J 6.8), 7.63 (1H, dd, ^3J 5.0, ^4J 1.2), 7.14 (1H, dd, ^3J 5.0 and 3.8) and 6.10 (1H, d, ^3J 6.8); δ_C 160.98 (q), 157.60 (q), 154.75, 133.74, 133.34 (q), 132.76, 128.52 and 108.36; *m/z* 179 (M^+, 59%), 151 (27), 127 (19), 113 (13), 112 (18), 111 (100), 83 (22) and 57 (14).

2-Carbomethoxy-6*H*-1,3-oxazin-6-one 166g {2,2-dimethyl-5-[*N*-(2-carbomethoxyamido)-], 500 °C, 225 °C, 0.01 Torr, 37 min, 0.5 g}, (80%), mp 93-95°C [sublimed at 155°C (0.5 Torr)], (Found: C, 46.25; H, 3.65; N, 9.1. $C_6H_5NO_4$ requires C, 46.45;

H, 3.25; N, 9.05); δ_H ([$^2H_6$]DMSO) 7.98 (1H, d, ^3J 6.8), 6.66 (1H, d, ^3J 6.8) and 3.88 (3H, s); δ_C ([$^2H_6$]DMSO) 157.66 (q), 157.02 (q), 153.69, 153.53 (q), 114.50 and 53.75; *m/z* 155 (M^+, 3%), 154 (10), 128 (17), 114 (10), 96 (100), 95 (28), 70 (13), 69 (12) and 59 (10).

4. Preparation of [5-^{2}H]-6*H*-1,3-Oxazin-6-ones[118]

Method

The appropriate 5-(*N*-amidomethylidene) Meldrum's acid derivative (1 mmol) was dissolved in [^{2}H]methanol (10 cm^3) by heating. The solution was allowed to stand for 15 min and the solvent was then removed under reduced pressure at the oil pump. The crude, deuteriated solid was immediately pyrolysed (inlet tube flame dried) and the product was extracted with deuteriated chloroform for spectroscopic examination. The following oxazinones were prepared. The amidomethylidene Meldrum's acid precursor and pyrolysis conditions for each example are given in brackets.

[5-^{2}H]-6*H*-1,3-oxazin-6-one 167b [2,2-dimethyl-5-(*N*-formamido-), 450 °C, 250 °C, 0.02 Torr, 8 min, 0.199 g], (90% deuterium incorporation); δ_H 7.94 (1H, d, ^4J 0.6) and 7.65 (1H, d, ^4J 0.6); δ_C 159.20 (q), 156.73 and 152.89.

2-Methyl-[5-^{2}H]-6*H*-1,3-oxazin-6-one 167a [2,2-dimethyl-5-(*N*-acetamido-), 500 °C, 150 °C, 0.02 Torr, 12 min, 0.213 g], (93% deuterium incorporation); δ_H 7.52 (1H, s) and 2.31 (3H, s); δ_C 168.21 (q), 158.20 (q), 153.64 and 21.24.

E. AMIDE PROTECTING GROUPS - SECONDARY ACYCLIC AMIDES AND UREAS

1. Preparation of *N,N,N'*-Trimethylurea[130,131]

Method

Dry, gaseous methylamine (generated by heating 30% aqueous methylamine solution and passing the vapour produced over sodium hydroxide pellets) was bubbled through an ice-cooled solution of dimethylcarbamoyl chloride (13.0 g, 0.12 moles) in ether (200 cm^3) for 30 min. The precipitate formed was collected by filtration and added to ether (100 cm^3). The mixture was heated until no more solid dissolved and then hot filtered to remove the insoluble methylamine hydrochloride. The solvent was removed from the filtrate to give the crude product which was recrystallised (1.94 g, 16%), mp 72-73 °C (from ether) (lit.,[130] 73-74 °C); δ_H 6.22 (1H, br s), 2.81 (6H, s) and 2.60 (3H, d, ^3J 4.4).

2. Reactions of Secondary Acyclic Amides and Ureas With 5-Methoxymethylidene Meldrum's Acid

Method

(a) The appropriate amide or urea (10 mmol) was dissolved in acetonitrile (50 cm^3) and 5-methoxymethylidene Meldrum's acid (1.86 g, 10 mmol) was added. The mixture was heated under reflux for the time quoted and then the solvent was removed under reduced pressure. The crude product was purified by either recrystallisation or dry flash chromatography (using *n*-hexane and ethyl acetate as eluents). The following derivatives were prepared. The secondary acyclic amide or urea used, reflux time and method of purification for each example are given in brackets.

2,2-Dimethyl-5-(*N*-formyl-*N*-methylaminomethylidene)-1,3-dioxane-4,6-dione 172 (*N*-methylformamide, 17 h, recrystallisation), (57%), mp 141-142 °C (from hexane/toluene), (Found: C, 50.65; H, 5.45; N, 6.5. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.55 %); δ_H 8.73 (1H, s), 8.44 (1H, s), 3.39 (3H, s) and 1.73 (6H, s); δ_C 164.58, 163.44 (q), 158.64 (q), 154.37, 104.22 (q), 96.04 (q), 33.94 and 26.92; *m/z* 213 (M^+, 3%), 156 (14), 155 (18), 128 (29), 127 (30), 99 (26), 84 (21), 83 (100), 82 (81), 81 (13) and 59 (12).

2,2-Dimethyl-5-(*N*-methyl-*N*-methylcarbamoylaminomethylidene)-1,3-dioxane-4,6-dione 183a (*N,N'*-dimethylurea, 7 h, recrystallisation), (48%), mp 158-159 °C (from toluene/ethyl acetate), (Found: C, 49.5; H, 5.85; N, 11.3. $C_{10}H_{14}N_2O_5$ requires C, 49.6; H, 5.85; N, 11.55%); δ_H 8.84 (1H, s), 6.65 (1H, br), 3.39 (3H, s), 2.92 (3H, d, ^3J 4.8) and 1.71 (6H, s); δ_C 164.63 (q), 159.71 (q), 155.65, 154.83 (q), 103.85 (q), 91.47 (q), 38.20, 28.24 and 26.80; *m/z* 185 (M^+ - C_3H_5O, 38%), 140 (10), 128 (31), 127 (33), 99 (38), 84 (25), 83 (100), 82 (31).

2,2-Dimethyl-5-(*N*-methyl-*N*-dimethylcarbamoylaminomethylidene)-1,3-dioxane-4,6-dione 183b (*N,N,N´*-trimethylurea,[130,131] 6 h, chromatography), (10%), bp 70 °C (0.6 Torr), (Found: M^+, 256.1054. $C_{11}H_{16}N_2O_5$ requires *M*, 256.1059); δ_H 8.07 (1H, br), 3.38 (3H, s), 2.94 (6H, s) and 1.66 (6H, s); δ_C (measured at -60 °C due to the broadness of the room temperature spectrum) 164.82 (q), 161.17 (q), 156.85, 156.09 (q), 103.99 (q), 90.01 (q), 44.16, 38.36, 36.23, 26.94 and 25.99; *m/z* 256 (M^+, 46%), 212 (38), 199 (41), 198 (66), 180 (20), 154 (38), 142 (27), 141 (30), 126 (56), 97 (43) and 72 (100).

(b) If the reflux was allowed to continue for the times quoted below, the Meldrum's acid derivatives, formed as above, reacted with the methanol by-product to give enamides, which were isolated by either dry flash chromatography (eluting with *n*-hexane and ethyl acetate) or recrystallisation. The following compounds were prepared. The secondary acyclic amide or urea used, method of isolation of product and reflux time for each example are given in brackets.

Methyl 3-(*N*-formyl-*N*-methylamino)prop-2-enoate 174a (*N*-methylformamide, 75 h, chromatography), (11%), mp 85-86 °C (from ethanol), (Found: C, 49.95; H, 6.75; N, 9.5. $C_6H_9NO_3$ requires C, 50.35; H, 6.35; N, 9.8 %); δ_H 8.42 (1H, s), 7.76 (1H, d, ^3J 13.5), 5.36 (1H, d, ^3J 13.5), 3.68 (3H, s) and 3.01 (3H, s); δ_C 166.98 (q), 162.98, 143.52, 99.22, 51.29 and 27.47; *m/z* 143 (M^+, 7%), 125 (10), 115 (15), 112 (11) and 84 (27).

Methyl 3-(*N*-methyl-*N*-carbamoylamino)prop-2-enoate 174b (*N,N´*-dimethylurea, 96 h, recrystallisation), (48%), mp 114-115 °C (from hexane/ethyl acetate), (Found: C, 48.6; H, 7.1; N, 16.4. $C_7H_{12}N_2O_3$ requires C, 48.85; H, 7.05; N, 16.25%); δ_H 8.21 (1H, d, ^3J 13.7), 5.85 (1H, br), 5.06 (1H, d, ^3J 13.7), 3.68 (3H, s), 3.06 (3H, s)

and 2.85 (3H, d, ^3J 4.4); δ_C 168.52 (q), 155.44 (q), 143.21, 95.17, 51.10, 31.11 and 27.80; *m/z* 172 (M^+, 3%), 141 (9), 115 (62), 84 (100), 83 (19), 82 (15) and 58 (27).

Methyl 3-(*N*-dimethylcarbamoyl-*N*-methylamino)prop-2-enoate 174c (*N,N,N'*-trimethylurea,[130,131] 16 h, chromatography), (8%), bp 65 °C (0.2 Torr), (Found: M^+, 186.1009. $C_8H_{14}N_2O_3$ requires *M*, 186.1004); δ_H 7.72 (1H, d, ^3J 13.6), 4.99 (1H, d, ^3J 13.6), 3.65 (3H, s), 2.96 (3H,s) and 2.87 (6H, s); δ_C 168.29 (q), 160.52 (q), 146.36, 94.13, 51.04, 38.53, 36.22 and 33.44; *m/z* 186 (M^+, 52%), 155 (46), 132 (27), 127 (50), 113 (54), 112 (51), 102 (43), 86 (74), 84 (87), 82 (40) and 72 (100).

All of the reactions consistently produced the same by-product in small amounts (30-100 mg) which could be isolated from the column, always eluting first. This was identified from spectra as trimethyl 1,3,5-benzenetricarboxylate **175** mp 140-141 °C (lit.,[181] 141-142 °C); δ_H 8.81 (3H, s) and 3.94 (9H, s); δ_C 165.19 (q), 134.37, 131.01 (q) and 52.44; *m/z* 252 (M^+, 10%), 222 (6), 221 (43), 193 (6), 44 (42) and 40 (100).

Reactions with *N*-methylacetamide and *N*-methylbenzamide under these sets of conditions failed to give any identifiable products other than unreacted starting material, even after dry flash column chromatography.

3. Pyrolyses of Secondary Acyclic 5-(*N*-Amidomethylidene) Meldrum's Acid Derivatives and Related Compounds

Method

The appropriate derivative was pyrolysed as described in Section D. Upon completion of the pyrolysis the entire pyrolysate was dissolved in solvent to enable removal from the trap.

(a) Pyrolysis of 2,2-Dimethyl-5-(*N*-formyl-*N*-methylaminomethylidene)-1,3-dioxane-4,6-dione 172 (600 °C, 180 °C, 0.01 Torr, 15 min, 0.19 g)

Examination of the pyrolysate by ^{1}H NMR spectroscopy showed no identifiable products. Repeat pyrolyses at higher and lower furnace temperatures (500-800 °C) gave the same result.

(b) Pyrolysis of 2,2-Dimethyl-5-(*N*-methyl-*N*-methylcarbamoylaminomethylidene)-1,3-dioxane-4,6-dione 183a (700 °C, 190 °C, 0.02 Torr, 55 min, 0.3 g)

The pyrolysate was removed from the trap with acetone from which a dark brown solid slowly precipitated. This was collected by filtration and shown to be N,N´-dimethyluracil **188** (0.02 g, 11%), mp 122-123 °C (from ethanol) (lit.,[193] 123-124 °C); δ_H[178] ([$^2H_6$]DMSO) 7.72 (1H, d, ^3J 7.9), 5.72 (1H, d, ^3J 7.9), 3.35 (3H, s) and 3.21 (3H, s).

(c) Pyrolysis of 2,2-Dimethyl-5-(*N*-methyl-*N*-dimethylcarbamoylaminomethylidene)-1,3-dioxane-4,6-dione 183b (700 °C, 150 °C, 0.01 Torr, 28 min, 0.1 g)

The pyrolysis produced mainly insoluble brown polymer. Examination of the minor soluble product(s) by ^{1}H NMR spectroscopy showed their to be a negligible amount of material and no identifiable products.

4. Attempted Methylation of 5-(*N*-Acetamidomethylidene) Meldrum's Acid

Method[90]

The four sets of reaction conditions listed below were all tried in an attempt to methylate 5-(*N*-acetamidomethylidene) Meldrum's acid at the nitrogen atom.

(i) Sodium hydride (2 x excess)/methyl iodide (5 x excess)/DMSO/24 h at room temperature

(ii) Sodium hydride (4 x excess)/methyl iodide (10 x excess)/DMSO/96 h at room temperature

(iii) Sodium hydride (2 x excess)/methyl *p*-toluenesulfonate (5 x excess)/DMSO/5 h at 90 °C

(iv) Hünig's base (2 x excess)/methyl *p*-toluenesulfonate (2 x excess)/DMSO/5 h at 90 °C

All failed to methylate the compound and starting material was quantitatively recovered from each reaction.

5. Attempted Acylation of 5-(*N*-Methylaminomethylidene) Meldrum's Acid

(a) Acetyl chloride

To a solution of 5-*N*-(methyl)aminomethylidene Meldrum's acid[90] (0.09 g, 0.5 mmol) in acetonitrile (40 cm^3) was added triethylamine (0.05 g, 0.5 mmol) and acetyl chloride (0.04 g, 0.5 mmol). The mixture was heated under reflux for 96 h and then the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (30 cm^3) and extracted with water (3 x 30 cm^3). The organic layer was washed with dilute hydrochloric acid (2M, 1 x 30 cm^3) and the combined aqueous washings were back-extracted with dichloromethane (2 x 30 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Examination of the crude solid obtained by ^1H NMR spectroscopy showed it to be unreacted starting material only.

(b) Benzoyl chloride

5-(*N*-Methylaminomethylidene) Meldrum's acid (0.37 g, 2 mmol) was dissolved in acetonitrile (50 cm^3). To this solution was added Hünig's base (1.295 g, 10 mmol) and benzoyl chloride (1.405 g, 10 mmol) and the mixture was heated under reflux for 5 days. The solvent was then removed under reduced pressure and the residue dissolved in dichloromethane (50 cm^3). The solution was washed with water (3 x 50 cm^3), dilute hydrochloric acid (2M, 1 x 50 cm^3) and dilute sodium hydroxide (2M, 1 x 50 cm^3). The organic layer was then dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue was subjected to dry flash chromatography using *n*-hexane, ethyl acetate and methanol as eluents. Three compounds were isolated from the column.

The first compound isolated was benzoic anhydride **191** [27% (based on 1 mole of benzoyl chloride giving 0.5 moles of product)], mp 40-41 °C (from column), (lit.,[179] 42 °C); δ_H 8.09-8.04 (4H, m) and 7.62-7.39 (6H, m); δ_C 162.19 (q), 134.39, 130.38, 128.72 and 128.71 (q); *m/z* 226 (M^+, 7%), 198 (21), 122 (6), 107 (33), 106 (100), 105 (38), 77 (89), 51 (43) and 50 (16).

The second and third compounds were isolated as a mixture which was shown to consist of benzoic acid and *N*-benzoyl-*N*-methylbenzamide. The latter was separated from the former using a basic work-up to give pure *N*-benzoyl-*N*-methylbenzamide **192** [30% (based on the Meldrum's acid derivative)], mp 92-94 °C, (lit.,[132] 94.5-94.8 °C); δ_H 7.45-7.40 (4H, m), 7.30-7.11 (6H, m) and 3.47 (3H, s); δ_C 174.25 (q), 135.78 (q) 131.65, 128.58, 128.08 and 34.07; *m/z* 239 (M^+, 11%), 212 (14), 105 (100), 77 (60) and 51 (22).

Further attempts at this reaction to produce the acylated product, using varying amounts of benzoyl chloride failed. Using benzoyl chloride itself as the reaction solvent resulted only in decomposition.

F. AMIDE PROTECTING GROUPS - SECONDARY CYCLIC AMIDES AND UREAS

1. Preparations of Cyclic Amides

(a) 6-Methylpiperidin-2-one[146]

A solution of methylmagnesium bromide in ether (2.7 cm^3, 8 mmol, 3M solution) was added to glutarimide (0.904 g, 8 mmol) in dry tetrahydrofuran (40 cm^3) under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min and then methylmagnesium bromide in ether (5.4 cm^3, 16 mmol, 3M solution) was added. The mixture was stirred for a further 2 h and then ethanol (40 cm^3), sodium cyanoborohydride (0.504 g, 8 mmol) and bromocresol green indicator were added. The lilac coloured solution was neutralised with 1% HCl in ethanol (until it was yellow in colour) and then stirred overnight. Water (100 cm^3) was then added, the solution became green and the mixture was extracted with chloroform (4 x 100 cm^3). The combined organic extracts were washed with water (150 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford the desired product **226b** which was recrystallised (0.338 g, 37%), mp 85-87 °C (from ethanol) (lit.,[146] 87-88 °C); δ_H 6.44 (1H, br), 3.47 (1H, m), 2.25 (2H, m), 1.95-1.20 (4H, m) and 1.15 (3H, d, ^3J 6.4); δ_C 172.39 (q), 48.61, 30.84, 30.26, 22.62 and 19.67.

(b) 6-Phenylpiperidin-2-one[144]

To a three necked flask equipped with a 10 cm Vigreux column and a dropping funnel was added ammonium carbonate (18.0 g). Formic acid (90% aqueous solution, 19.0 g) was added dropwise with stirring over a period of 15 min and the mixture was slowly heated to 60 °C. When the initial reaction had subsided the temperature was increased to 165 °C and maintained for 2 h. 4-Benzoylbutyric acid

(9.4 g, 0.49 mol) was then added all at once and the mixture heated at 165 °C for a further 24 h. During this time excess water, ammonia, formic acid and methylamine distilled slowly out of the mixture and ammonium carbonate and carbamate deposited in the condenser. The residual orange/brown reaction mixture was then cooled to room temperature. The mixture was rotary evaporated under high vacuum (~1 Torr) (with a hot water bath) to remove the volatiles. Crystallisation occurred over a period of 24 h, with an initial period at -20 °C. The solid was collected by filtration, and washed with hexane and then repeatedly recrystallised from hexane to give the desired product **226a** (3.81 g, 41%), mp 140-141 °C (from hexane) (lit.,[144] 141-142 °C); δ_H 7.35-7.24 (5H, m), 4.50 (1H, m), 2.40-2.34 (2H, m), 2.04 (1H, m) and 1.84-1.59 (3H, m); δ_C 172.33 (q), 142.35 (q), 128.49, 127.56, 125.83, 57.27, 31.78, 30.98 and 19.22.

(c) 3,4-Dihydroisoquinolin-1(2*H*)-one[138]

(i) A solution of ethyl chloroformate (11.0 g, 0.105 mol) in chloroform (50 cm^3) was added dropwise to an ice-cooled, stirred solution of 2-phenylethylamine (12.0 g, 0.1 mol) and triethylamine (10.0 g) in chloroform (25 cm^3). The resulting mixture was stirred for 1 h at room temperature and the solvent was then removed under reduced pressure. Ether (250 cm^3) was added to the residue to precipitate triethylamine hydrochloride, which was removed by filtration. The solvent was removed from the filtrate under reduced pressure and the resulting oil was distilled to give ethyl *N*-(2-phenethyl)carbamate **205** (17.07 g, 89%), bp 97-98 °C (0.3 Torr) [lit.,[138] 114 °C (0.6 Torr)]; δ_H 7.90-7.35 (5H, m), 5.35 (1H, br s), 4.50 (2H, q, ^3J 7.0), 3.80 (2H, q, ^3J 6.0), 3.2 (2H, t, ^3J 6.0) and 1.60 (3H, t, ^3J 7.0).

(ii) A stirred mixture of ethyl *N*-(2-phenethyl)carbamate (7.5 g, 0.054 mol) and polyphosphoric acid (75 g) was heated at 120 °C for 1.5 h. The mixture was then poured into water (100 cm^3) and extracted with chloroform (3 x 50 cm^3). The

combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The oil obtained was purified by Kugelrohr distillation to give the title compound **202** (3.47 g, 61%), bp 150-155 °C (0.4 Torr) [lit.,[138] 150 °C (0.4 Torr)]; δ_H 8.10 (1H, br), 8.00 (1H, m), 7.51-7.20 (2H, m), 7.16 (1H, m), 3.68-3.34 (2H, m) and 2.89 (2H, t, ^3J 6.0); δ_C 166.63 (q), 138.62 (q), 131.66, 128.67 (q), 127.30, 126.88, 126.57, 39.57 and 27.80; *m/z* 147 (M^+, 74%), 119 (10), 118 (100), 91 (10), 90 (44) and 89 (16).

(d) 2,3-Dihydroisoindol-1(1*H*)-one[139]

N-Bromosuccinimide (28.5 g, 0.16 mol) and dibenzoyl peroxide (0.32 g, 1.25 mmol) were added to a solution of methyl *o*-toluate (22.5 g, 0.165 mol) in carbon tetrachloride (90 cm^3). The mixture was heated under reflux, with stirring, for 4 h and then was allowed to cool to room temperature. The succinimide which precipitated was removed by filtration and the solvent was removed from the filtrate under reduced pressure. The residual yellow oil was dissolved in methanol (125 cm^3) and concentrated (aqueous) ammonia (40 cm^3) was added. The mixture was brought to reflux and ammonia gas was bubbled through the refluxing solution for 2 h. The mixture was then cooled and the volatiles were removed under reduced pressure. The remaining yellow solid obtained was washed thoroughly with water and then with ether and the crude material was recrystallised to give the title compound **207** (8.69 g, 44%), mp 148-149 °C (from H_2O) (lit.,[180] 150-151 °C); δ_H 8.52 (1H, br), 7.82 (1H, m), 7.62-7.40 (3H, m) and 4.44 (2H, s); δ_C 172.24 (q), 143.54 (q), 131.74 (q), 131.45, 127.68, 123.31, 122.95 and 45.72.

2. Preparation of Cyclic 5-(*N*-amidomethylidene) Meldrum's Acid Derivatives and Related Compounds

Method

(a) The appropriate cyclic amide or urea (10 mmol) was dissolved in acetonitrile (50 cm^3) and 5-methoxymethylidene Meldrum's acid (1.86 g, 10 mmol) was added. The mixture was heated under reflux for the time quoted below and then the solvent was removed under reduced pressure to give the crude, solid product which could be recrystallised. The following Meldrum's acid derivatives were prepared. The cyclic amide or urea used and reflux time for each example are given in brackets.

2,2-Dimethyl-5-[*N*-(2-oxopyrrolidinyl)methylidene]-1,3-dioxane-4,6-dione 199a (pyrrolidin-2-one, 8 h), (74%), mp 134-135 °C (from hexane/toluene), (Found: C, 55.4; H, 5.75; N, 5.8. $C_{11}H_{13}NO_5$ requires C, 55.25; H, 5.5; N, 5.85 %); δ_H 8.69 (1H, s), 4.06 (2H, m), 2.59 (2H, t, ^3J 8.1), 2.23-2.10 (2H, m) and 1.71 (6H, s); δ_C 175.90 (q), 163.67 (q), 159.23 (q), 147.20, 103.93 (q), 94.73 (q), 49.51, 29.58, 26.88 and 18.04; *m/z* 181 (M^+ - C_3H_6O, 100%), 153 (36), 138 (11), 109 (65), 108 (21), 82 (17), 81 (61), 80 (29) and 68 (16).

2,2-Dimethyl-5-[*N*-(5-methyl-2-oxopyrrolidinyl)methylidene]-1,3-dioxane-4,6-dione 199b (5-methylpyrrolidin-2-one, 8 h), (67%), mp 139-140 °C (from hexane/toluene), (Found: C, 56.95; H, 6.2; N, 5.5. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 5.95; N, 5.55 %); δ_H 8.62 (1H, s), 5.34-5.22 (1H, m), 2.73-2.50 (2H, m), 2.41-2.11 (1H, m), 1.88-1.77 (1H, m), 1.70 (3H, s), 1.68 (3H, s) and 1.10 (3H, d, ^3J 6.4); δ_C 175.62 (q), 163.77 (q), 159.17 (q), 145.89, 103.77 (q), 94.65 (q), 54.66, 28.12, 27.20, 26.41, 24.89 and 19.17; *m/z* 195 (M^+ - C_3H_6O, 100%), 167 (17), 149 (11), 123 (44), 122 (83), 96 (54), 95 (26), 94 (43), 81 (15), 68 (33) and 67 (28).

2,2-Dimethyl-5-[*N*-(2-oxopiperidinyl)methylidene]-1,3-dioxane-4,6-dione 199c (piperidin-2-one, 8 h), (59%), mp 143-144 °C (from hexane/toluene), (Found: C, 56.7; H, 6.05; N, 5.45. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 5.95; N, 5.55%); δ_H 9.00 (1H, s), 3.78 (2H, t, ^3J 5.8), 2.68 (2H, t, ^3J 6.7), 1.96-1.86 (4H, m) and 1.70 (6H, s); δ_C 170.52 (q), 163.59 (q), 159.07 (q), 152.59, 103.80 (q), 96.28 (q), 51.87, 32.76, 26.86, 22.69 and 19.76; *m/z* 195 (M^+ - C_3H_6O, 93%), 167 (43), 151 (26), 139 (71), 127 (34), 123 (47), 109 (31), 95 (71), 94 (60), 82 (32) and 67 (100).

2,2-Dimethyl-5-[*N*-(2-oxoimidazolidinyl)methylidene]-1,3-dioxane-4,6-dione 199d (imidazolidin-2-one, 7 h), (58%), mp 192-193 °C (dec.) (from ethanol/ acetonitrile), (Found: C, 49.75; H, 5.35; N, 11.4. $C_{10}H_{12}N_2O_5$ requires C, 50.0; H, 5.05; N, 11.65%); δ_H ([$^2H_6$]DMSO) 8.58 (1H, br), 8.47 (1H, s), 4.12 (2H, t, ^3J 7.5), 3.45 (2H, t, ^3J 7.5) and 1.66 (6H, s); δ_C ([$^2H_6$]DMSO) 164.45 (q), 159.49 (q), 155.27 (q), 148.78, 103.62 (q), 89.87 (q), 45.68, 37.26 and 26.48; *m/z* 240 (M^+, 8%), 183 (29), 182 (100), 139 (37), 138 (23), 110 (53), 82 (29), 70 (22) and 67 (34).

2,2-Dimethyl-5-[*N*-(1-oxo-3,4-dihydroisoquinolinyl)methylidene]-1,3-dioxane-4,6-dione 199e (3,4-dihydroisoquinolin-1(2*H*)-one, 18 h), (64%), mp 186-187 °C (from toluene), (Found: C, 63.65; H, 5.05; N, 4.5. $C_{16}H_{15}NO_5$ requires C, 63.8; H, 5.0; N, 4.65%); δ_H 9.24 (1H, s), 8.09 (1H, m), 7.59-7.25 (3H, m), 4.14 (2H, t, ^3J 6.0), 3.10 (2H, t, ^3J 6.0), and 1.75 (6H, s); δ_C 163.60 (q), 163.25 (q), 159.39 (q), 153.41, 139.61 (q), 134.33, 130.10, 127.73, 127.35, 126.41 (q), 103.89 (q), 95.88 (q), 50.27, 27.94 and 27.09; *m/z* 243 (M^+ - C_3H_6O, 100%), 214 (81), 199 (42), 198 (25), 171 (38), 170 (56), 132 (37) and 118 (30).

2,2-Dimethyl-5-[*N*-(1-oxo-2,3-dihydroisoindolyl)methylidene]-1,3-dioxane-4,6-dione 199f (2,3-dihydroisoindol-1(1*H*)-one, 6 h), (60%), mp 196-197 °C (dec.) (from toluene/ethyl acetate), (Found: C, 62.45; H, 4.75; N, 4.6. $C_{15}H_{13}NO_5$ requires C, 62.7; H, 4.55; N, 4.9%); δ_H 9.04 (1H, s), 7.97 (1H, m), 7.73 (1H, m), 7.57-7.50 (2H, m), 5.29 (2H, s) and 1.75 (6H, s); δ_C 167.79 (q), 163.80 (q), 159.82 (q), 146.95,

142.96 (q), 135.47, 129.02, 126.92 (q), 125.77, 123.37, 104.04 (q), 94.51 (q), 52.42 and 27.03; *m/z* 287 (M^+, 4%), 280 (26), 231 (31), 230 (68), 229 (100), 202 (37), 201 (70), 186 (64), 185 (77), 157 (85), 149 (62), 133 (71) and 104 (75).

Reactions with 6-methylpiperidinone and 6-phenylpiperidinone under these sets of conditions failed to give any identifiable products other than unreacted starting material and 5-hydroxymethylidene Meldrum's acid, even after dry flash column chromatography.

(b) If the reflux was allowed to continue for the times quoted below, the Meldrum's acid derivative, formed as above, reacted with the methanol by-product to give enamides, which were isolated by either dry flash column chromatography (eluting with *n*-hexane and ethyl acetate) or recrystallisation. The following compounds were prepared. The cyclic amide used, method of isolation of product and reflux time for each example is given in brackets.

Methyl 3-[*N*-(2-oxopyrrolidinyl)]prop-2-enoate 200a (pyrrolidin-2-one, chromatography, 72 h), (19%), mp 83-84 °C (from hexane/toluene), (Found: C, 56.95; H, 6.85; N, 8.15. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.55; N, 8.3 %); δ_H 8.01 (1H, d, ^3J 14.3), 5.13 (1H, d, ^3J 14.3), 3.65 (3H, s), 3.49 (2H, t, ^3J 7.2), 2.47 (2H, t, ^3J 7.8) and 2.15-2.05 (2H, m); δ_C 174.02 (q), 167.34 (q), 137.14, 99.85, 51.08, 44.65, 30.62 and 17.10; *m/z* 169 (M^+, 100%), 138 (37), 137 (13), 114 (8), 110 (42), 82 (49) and 70 (17).

Methyl 3-[*N*-(5-methyl-2-oxopyrrolidinyl)]prop-2-enoate 200b (5-methylpyrrolidin-2-one, chromatography, 138 h), (26%), bp 105 °C (0.7 Torr), (Found: M^+, 183.0907. $C_9H_{13}NO_3$ requires *M*, 183.0895); δ_H 7.93 (1H, d, ^3J 14.5), 5.21 (1H, d,

^3J 14.5), 4.00 (1H, m), 3.66 (3H, s), 2.63-2.16 (3H, m), 1.81-1.66 (1H, m) and 1.21 (3H, d, ^3J 6.4); δ_C 173.73 (q), 167.51 (q), 136.18, 99.85, 51.09, 52.23, 29.15, 25.60 and 17.63; *m/z* 183 (M^+, 68%), 168 (42), 152 (69), 151 (27), 124 (95), 108 (17), 96 (100), 83 (20) and 70 (34).

Methyl 3-[*N*-(2-oxopiperidinyl)]prop-2-enoate 200c (piperidin-2-one, chromatography, 54 h), (50%), mp 91-93 °C (from hexane/toluene), (Found: C, 58.7; H, 7.4; N, 7.35. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.15; N, 7.65%); δ_H 8.55 (1H, d, ^3J 14.5), 5.21 (1H, d, ^3J 14.5), 3.67 (3H, s), 3.38 (2H, t, ^3J 6.2), 2.50 (2H, t, ^3J 6.4) and 1.94-1.76 (4H, m); δ_C 169.12 (q), 167.64 (q), 140.68, 99.18, 52.12, 45.39, 32.90, 22.09 and 19.98; *m/z* 183 (M^+, 4%), 152 (16), 124 (100), 96 (11), 95 (11), 82 (23) and 55 (12).

Methyl 3-[*N*-(2-oxoimidazolidinyl)]prop-2-enoate 200d (imidazolidin-2-one, recrystallisation, 192 h), (58%), mp 147-148 °C (from hexane/ethyl acetate), (Found: C, 49.45; H, 6.0; N, 16.75. $C_7H_{10}N_2O_3$ requires C, 49.4; H, 5.9; N, 16.45%); δ_H 8.01 (1H, d, ^3J 14.3), 6.5 (1H, br), 4.94 (1H, d, ^3J 14.3), 3.68 (3H, s) and 3.66-3.60 (4H, m); δ_C 167.85 (q), 157.35 (q), 138.86, 95.45, 51.04, 41.79 and 37.32; *m/z* 170 (M^+, 49%), 139 (81), 138 (100), 111 (27), 96 (24), 95 (66), 82 (88), 70 (28), 69 (25) and 68 (43).

Methyl 3-[*N*-(3,4-dihydro-1-oxoisoquinolinyl)]prop-2-enoate 200e (3,4-dihydroisoquinolin-1(2*H*)-one, chromatography, 120 h), (26%), mp 140-141 °C (from hexane/toluene), (Found: C, 67.8; H, 6.05; N, 6.0. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%); δ_H 8.66 (1H, d, ^3J 14.5), 8.05 (1H, m), 7.45 (1H, m), 7.32 (1H, m), 7.20 (1H, m), 5.36 (1H, d, ^3J 14.5), 3.70 (3H, s), 3.73 (2H, t, ^3J 6.6) and 3.06 (2H, t, ^3J 6.6); δ_C 167.71 (q), 162.50 (q), 140.82, 138.05 (q), 132.93, 129.08, 127.66 (q), 127.25, 127.00, 99.35, 51.16, 42.88 and 26.78; *m/z* 231 (M^+, 14%), 200 (46), 173 (37), 172 (100), 130 (13), 118 (12), 91 (11), 90 (22) and 89 (13).

All of the reactions consistently produced the same by-product in small amounts (30-100 mg) which could be isolated from the column, always eluting first. This was identified from spectra as trimethyl 1,3,5-benzenetricarboxylate **175**, as reported earlier in Section E, part 2.

3. Pyrolyses of Cyclic 5-(*N*-amidomethylidene) Meldrum's Acid Derivatives and Related Compounds

Method

The appropriate Meldrum's acid derivative was pyrolysed as described in Section D. After pyrolysis, involatile solid products were scraped from the trap, whereas volatile solids and liquids were washed from the trap with solvent. After the solvent had been removed under reduced pressure, the crude pyrolysate was purified by either recrystallisation, Kugelrohr distillation or dry flash column chromatography (using ethyl acetate and *n*-hexane as eluents). The following compounds were pyrolysed, with the pyrolysis conditions for each example given in brackets. In some of the following cases the product could exist as a tautomeric mixture. The data quoted is always for the major tautomer, and in practice this was the only one observed.

2,2-Dimethyl-5-[*N*-(2-oxopyrrolidinyl)methylidene]-1,3-dioxane-4,6-dione 199a

[700 °C, 170 °C, 0.02 Torr, 150 min, 1.79 g]

Pyrolysis produced *7-hydroxy-1*H*-pyrrolizin-3(2*H*)-one*‡ **212** which was purified by recrystallisation, (62%), mp 149-150 °C (dec.) (from ethyl acetate/methanol), (Found: C, 61.1; H, 5.1; N, 9.95. $C_7H_7NO_2$ requires C, 61.3; H, 5.15; N, 10.2%); δ_H ([$^2H_6$]DMSO) 8.57 (1H, s), 6.79 (1H, d, ^3J 3.1), 6.09 (1H, d, ^3J 3.1), and 2.95-2.75 (4H, m); δ_C ([$^2H_6$]DMSO) 171.71 (q), 137.89 (q), 118.28 (q), 113.01, 108.09, 34.43 and 17.83; *m/z* 137 (M^+, 98%), 109 (16), 108 (19), 96 (20), 95 (100), 81 (17), 80 (38), 68 (15) and 67 (29).

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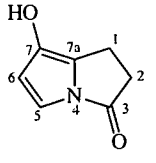
‡ The numbering scheme used in the compound shown is based on the 1*H*-pyrrolizin-3-one system, with the amide carbonyl taking precedence over the hydroxyl group.



2,2-Dimethyl-5-[*N*-(5-methyl-2-oxopyrrolidinyl)methylidene]-1,3-dioxane-4,6-dione 199b [700 °C, 180 °C, 0.01 Torr, 90 min, 1.91 g]

Pyrolysis produced *7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione*‡ **210** which was purified by Kugelrohr distillation, (68%), mp 91-92 °C [sublimed at 145 °C (0.2 Torr)], (Found: C, 63.35; H, 5.95; N, 9.1. $C_8H_9NO_2$ requires C, 63.55; H, 6.0; N, 9.25%); δ_H 8.11 (1H, d, ^3J 4.0), 5.56 (1H, d, ^3J 4.0), 2.92 (1H, ddd, ^2J 17.4, ^3J 12.7 and 8.1), 2.53 (1H, dd, ^2J 17.4 and ^3J 7.7), 2.10-1.88 (2H, m) and 1.41 (3H, s); δ_C 205.27 (q), 172.45 (q), 152.99, 111.64, 69.09 (q), 34.40, 27.56 and 22.09; *m/z* 151 (M^+, 100%), 123 (27), 122 (17), 95 (43), 82 (19), 81 (60), 80 (32), 68 (26) and 67 (72).

2,2-Dimethyl-5-[*N*-(1-oxo-2,3-dihydroisoindolyl)methylidene]-1,3-dioxane-4,6-dione 199f [700 °C, 165 °C, 0.01 Torr, 180 min, 0.8 g]

Pyrolysis produced *1-hydroxy-5*H*-pyrrolo[2,1-*a*]isoindol-5-one* **213** which was purified by recrystallisation, (80%), mp 100-101 °C (from chloroform/hexane), (Found: C, 71.1; H, 4.1; N, 7.8. $C_{11}H_7NO_2$ requires C, 71.35; H, 3.8; N, 7.55%); δ_H ([$^2H_6$]Acetone) 9.02 (1H, br s), 7.60-7.39 (3H, m), 7.15 (1H, m), 6.95 (1H, d, ^3J 3.4) and 5.95 (1H, d, ^3J 3.4); δ_C ([$^2H_6$]Acetone) 160.86 (q), 142.39 (q), 135.24 (q), 133.46, 129.63 (q), 124.34 (2 x C), 118.35, 115.53, 114.50 (q) and 110.17; *m/z* 185 (M^+, 100%), 157 (18), 133 (24), 132 (13), 130 (10), 129 (12), 104 (12), 103 (18), 102 (12) and 76 (11).

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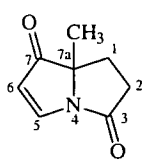
‡ The numbering scheme used in the compound shown is based on the 1*H*-pyrrolizin-3-one system, with the amide carbonyl taking precedence over the keto carbonyl.



2,2-Dimethyl-5-[*N*-(2-oxopiperidinyl)methylidene]-1,3-dioxane-4,6-dione 199c

[700 °C, 195 °C, 0.02 Torr, 90 min, 1.27 g]

Pyrolysis produced a complex mixture with a high proportion of the ^{1}H NMR integral of the spectrum over the alkyl region. This mixture was subjected to dry flash vacuum chromatography using *n*-hexane and ethyl acetate as eluents. The only identifiable product obtained was *8a-hydroxy-7,8-dihydroindolizine-1,5(6*H*,8a*H*)-dione* **215**, (14%), bp 120 °C (0.3 Torr), (Found: M^+, 167.0588. $C_8H_9NO_3$ requires *M*, 167.0582); δ_H 8.48 (1H, d, ^3J 4.4), 5.57 (1H, d, ^3J 4.4), 2.86-2.70 (1H, m), 2.65-2.06 (3H, m), 2.00-1.82 (1H, m) and 1.50-1.34 (1H, m); δ_C 201.42 (q), 168.17 (q), 154.89, 106.80, 84.63 (q), 29.88, 27.50 and 15.45; *m/z* 167 (M^+, 7%), 139 (59), 111 (60), 96 (57), 86 (49), 85 (41), 84 (88), 83 (74), 82 (46), 68 (66) and 42 (100).

2,2-Dimethyl-5-[*N*-(1-oxo-3,4-dihydroisoquinolinyl)methylidene]-1,3-dioxane-4,6-dione 199e [700 °C, 210 °C, 0.02 Torr, 120 min, 2.72 g]

Initial small scale pyrolyses carried out over a range of furnace temperatures (500-750 °C) showed little consistency when pyrolysates were examined by ^{1}H NMR spectroscopy. The most promising temperature was therefore selected and the pyrolysis scaled-up. Dry flash column chromatography of the soluble portion of the pyrolysate (using *n*-hexane and ethyl acetate as eluents) gave one identifiable product which was assigned as 2-ethenylsoquinolin-1(2*H*)-one[182] **237**, (2%), bp 80-85 °C (0.5 Torr); δ_H (360 MHz) 8.41 (1H, m), 7.70 (1H, dd, ^3J 9.2 and 16.1), 7.62 (1H, m), 7.46 (2H, m), 7.33 (1H, d, ^3J 7.6), 6.52 (1H, d, ^3J 7.6), 5.20 (1H, dd, ^2J 1.7 and ^3J 16.1) and 4.97 (1H, dd, ^2J 1.7, ^3J 9.2); δ_C (90 MHz) 160.67 (q), 136.31 (q), 132.64, 131.67, 128.23, 127.19, 126.10 (q), 125.99, 125.90, 107.11 and 101.19 (lit., δ_C[182] 160.74, 136.48, 132.69, 131.72, 128.32, 127.25, 126.13 (2 x C), 125.95, 107.16 and 107.13); *m/z* 171 (M^+, 74%), 170 (91), 169 (52), 147 (37), 146 (38), 145 (51), 130 (36), 129 (32), 128 (47), 119 (47), 118 (57), 117 (49), 116 (51), 115 (54), 102 (41) and 86 (100).

2,2-Dimethyl-5-[*N*-(2-oxoimidazolidinyl)methylidene]-1,3-dioxane-4,6-dione

199d [700 °C, 240 °C, 0.02 Torr, 27 min, 0.1 g]

Pyrolysis of this compound proved difficult due to its poor volatility. Pyrolysis of 0.1 g gave a black residue of 0.04 g in the inlet tube, and mainly insoluble polymeric material in the trap. Examination of the minor soluble portion of the pyrolysate by ^{1}H NMR spectroscopy showed it to be 1-ethenyl-1,3-dihydroimidazol-2(2*H*)-one[183,184] **241**, (4%), bp 100 °C (0.3 Torr), (Found: M^+, 110.0482. $C_5H_6N_2O$ requires *M*, 110.0480); δ_H 6.90 (1H, dd, ^3J 16.1 and 9.2), 6.48 (1H, m), 6.33 (1H, m), 4.89 (1H, dd, ^3J 16.1 and ^2J 1.1) and 4.65 (1H, dd, ^3J 9.2 and ^2J 1.1); δ_C ([$^2H_6$]DMSO) 164.32 (q), 127.33, 110.56, 107.15 and 95.62; *m/z* 110 (M^+, 78%), 86 (87), 85 (15), 82 (21), 81 (56), 73 (15), 68 (32), 57 (15), 56 (41), 55 (42), 54 (94) and 53 (17).

G. REACTIONS OF 7a-METHYL-1*H*-PYRROLIZINE-3,7(2*H*,7a*H*)-DIONE

1. *N*-Bromosuccinimide[149]

To a stirred solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.15 g, 1 mmol) in chloroform (5 cm^3) was added a solution of *N*-bromosuccinimide (0.175 g, 1 mmol) in chloroform (8 cm^3). The mixture was stirred at room temperature for 48 h and then poured into dichloromethane (20 cm^3) and extracted with saturated sodium hydrogen carbonate solution (3 x 20 cm^3). The combined aqueous washings were back-extracted with dichloromethane (2 x 20cm^3) and the combined organic layers were then dried ($MgSO_4$). The solvent was then removed under reduced pressure and the crude material subjected to dry flash chromatography using *n*-hexane and ethyl acetate as eluents to give *6-bromo-7a-methyl-1*H-*pyrrolizine-3,7(2*H,*7a*H)*-dione* **244** (62 mg, 27%), mp 134-135 °C (from hexane/ toluene), (Found: C, 41.6; H, 3.4; N, 5.9. $C_8H_8NO_2Br$ requires C, 41.75; H, 3.5; N, 6.1%); δ_H 8.28 (1H, s), 3.05-2.86 (1H, m), 2.65-2.58 (1H, m), 2.24-1.98 (2H, m) and 1.54 (3H, s); δ_C 198.34 (q), 171.52 (q), 151.56, 105.18 (q), 69.08 (q), 33.52, 27.77 and 22.61; *m/z* 231 (M^+, 20%), 229 (M^+, 26%), 196 (15), 150 (22), 122 (100), 119 (59), 110 (20), 105 (23), 99 (30) and 91 (46).

2. 5-Methoxymethylidene Meldrum's acid[149]

7a-Methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione failed to react with 5-methoxymethylidene Meldrum's acid even after prolonged periods of time in refluxing acetonitrile. Starting material was always quantitatively recovered.

3. Thiophenol[150]

A solution of thiophenol (0.108 g, 1 mmol) in methanol (10 cm^3) was added to a solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.15 g, 1 mmol) in methanol (10 cm^3). The mixture was stirred overnight at room temperature and the solvent was then removed under reduced pressure to give a crude solid which was recrystallised to give cis-*5,6-dihydro-7a-methyl-5-thiophenyl-1*H*-pyrrolizine-3,7(2*H*, 7a*H*)-dione* **246a** (0.227 g, 89%), mp 89-90 °C (from hexane/toluene), (Found: C, 64.25; H, 5.65; N, 5.35. $C_{14}H_{15}NO_2S$ requires C, 64.35; H, 5.8; N, 5.35%); δ_H 7.53 (2H, m), 7.32 (3H, m), 5.90 (1H, dd, ^3J 8.5 and 1.7), 3.11 (1H, dd, ^3J 8.5, ^2J 19.5), 2.74-2.61 (2H, m), 2.38-2.25 (1H, m), 2.09-2.00 (2H, m) and 1.62 (3H, s); δ_C 213.19 (q), 176.26 (q), 132.40 (q), 132.17, 128.95, 127.89, 67.89 (q), 56.72, 44.30, 31.53, 31.17 and 23.45; *m/z* 261 (M^+, 1%), 152 (21), 151 (27), 124 (35), 110 (100), 109 (33), 95 (18), 94 (21), 84 (23) and 81 (23).

4. Pyrrolidine

To a solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.302 g, 2 mmol) in methanol (10 cm^3) was added a solution of pyrrolidine (0.144 g, 2 mmol) in methanol (15 cm^3). The mixture was heated under reflux for 4 h, and the solvent was then removed under reduced pressure to give the crude product which was recrystallised to give *5-methyl-5-(1-oxo-3-pyrrolidinylprop-2-en-1-yl)pyrrolidin-2-one* **251** (0.393 g, 88%), mp 119-120 °C (from hexane/toluene), (Found: C, 64.9; H, 8.45; N, 12.35. $C_{12}H_{18}N_2O_2$ requires C, 64.85; H, 8.15; N, 12.6%); δ_H 7.70 (1H, d, ^3J 12.3), 7.40 (1H, br s), 5.04 (1H, d, ^3J 12.3), 3.34 (2H, m), 3.02 (2H, m), 2.31-2.12 (3H, m), 1.85-1.71 (5H, m) and 1.25 (3H, s); δ_C 197.08 (q), 177.23 (q), 149.93, 89.27, 65.74 (q), 51.88, 46.52, 32.20, 29.98, 25.51, 24.63 and 24.53; *m/z* 222 (M^+, 4%), 150 (11), 124 (75), 123 (37), 122 (12), 119 (29), 99 (40), 98 (67), 91 (27) and 84 (100).

5. Aniline

A solution of aniline (0.091 g, 1 mmol) in methanol (5 cm^3) was added to a stirred solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.15 g, 1 mmol) in methanol (10 cm^3). The mixture was stirred at room temperature for 24 h, during which time a white solid precipitated. The precipitate was removed by filtration and the solvent was removed from the filtrate to give a crude solid. The two solids were combined, washed with hexane and recrystallised to give cis-*5,6-dihydro-5-anilino-7a-methyl-1*H-*pyrrolizine-3,7(2*H,7a*H)-dione* **246b** (0.154 g, 64%), mp 188-189 °C (from toluene), (Found: C, 68.75; H, 6.7; N, 11.15. $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.6; N, 11.45%); δ_H 7.24 (2H, m), 6.97-6.80 (3H, m), 5.81 (1H, m), 4.01 (1H, br), 3.09 (1H, m), 2.80-2.32 (3H, m), 2.17-2.00 (2H, m) and 1.46 (3H, s); δ_C 214.58 (q), 177.39 (q), 144.47 (q), 129.27, 119.39, 113.77, 67.49 (q), 61.56, 45.17, 31.72, 31.15 and 24.19; *m/z* 244 (M^+, 4%), 146 (8), 125 (12), 124 (100), 119 (22), 118 (29) and 93 (63).

6. Hydrogenation

To a suspension of palladium on charcoal (5%, 0.03 g) in ethyl acetate (30 cm^3) was carefully added a solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione in ethyl acetate (10 cm^3). The mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and room temperature for 3.5 h. The mixture was then filtered through a celite pad and washed thoroughly with ethyl acetate. The solvent was removed from the filtrate, leaving a yellow oil which was purified by Kugelrohr distillation to give *5,6-dihydro-7a-methyl-1*H-*pyrrolizine-3,7(2*H,7a*H)-dione* **257** (0.151 g, 99%), bp 125 °C (0.3 Torr), (Found: M^+, 153.0791. $C_8H_{11}NO_2$ requires *M*, 153.0790); δ_H 4.20 (1H, m), 3.26 (1H, m), 2.79-2.50 (2H, m), 2.33 (1H, m), 2.16-1.88 (3H, m) and 1.29 (3H, s); δ_C 214.84 (q), 176.36 (q), 67.81 (q), 37.09, 36.68, 31.85, 29.30 and

20.98; *m/z* 153 (M^+, 4%), 125 (66), 110 (11), 98 (11), 97 (37), 82 (17), 69 (27), 56 (100), 55 (23) and 54 (12).

7. Photolysis[152]

A solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.25 g, 1.6 mmol) and benzophenone (0.301 g, 1.6 mmol) in acetonitrile (20 cm^3) was irradiated for 7 h with a 125 W mercury lamp. The solvent was then removed under reduced pressure and the solid residue subjected to dry flash column chromatography to remove the benzophenone. The remainder of the solid was shown to be a mixture of dimers by ^1H NMR spectroscopy. Fractional crystallisation using methanol allowed isolation of the major component *perhydro-8a-10a-dimethylcyclobuta[1,2-*e*:4,3-*e*']-1H-dippyrolizine-3,6,9,10(2H,7H,8aH,10aH)-tetraone* **260** (0.151 g, 30%), mp 328-330 °C (dec.) (from methanol), (Analyses reproducibly as partial hydrate. Found: C, 62.25; H, 6.05; N, 9.05. $C_{16}H_{18}N_2O_4.0.4H_2O$ requires C, 62.1; H, 6.1; N, 9.05%); δ_H (360 MHz, [$^2H_3$]Acetonitrile) 4.85 (1H, ddd, ^3J 6.7 and 1.8, ^4J 1.1), 4.29 (1H, m, ^3J 6.4 and 1.8, ^4J 0.8), 3.46 (1H, ddd, ^3J 6.4 and 4.1, ^4J 1.1), 3.18 (1H, ddd, ^3J 6.7 and 4.1, ^4J 0.8), 2.93-2.71 (2H, m), 2.42-2.05 (2H, m), 1.55 (3H, s) and 1.30 (3H, s); δ_C (360 MHz, [$^2H_3$]Acetonitrile) 214.70 (q), 208.45 (q), 176.89 (q), 172.46 (q), 69.93 (q), 69.14 (q), 56.04, 53.29, 47.69, 45.48, 32.40, 30.76, 30.73, 27.97, 25.02 and 21.57; *m/z* (FAB) 303 (MH^+, 100%), 301 (13), 152 (17), 151 (46), 150 (11), 123 (11), 98 (34), 97 (18), 95 (15), 93 (20), 91 (13), 90 (11), 89 (13), 83 (13), 81 (27), 79 (23), 77 (22), 73 (24) and 69 (31).

The minor components (<1%) remaining after fractional crystallisation were determined to be 2 symmetrical dimers, and were inseparable by dry flash chromatography. Consequently the ^1H and ^{13}C NMR spectra of the mixture of these two compounds are reported, δ_H ([$^2H_3$]Acetonitrile) 4.61 (2H, m), 4.51 (2H, m), 3.42

(2H, m), 3.28 (2H, m) and 2.52-1.90 (16H, m); δ_C ([$^2H_3$]Acetonitrile) 213.39 (q), 209.83 (q), 176.81 (q), 172.25 (q), 70.85 (q), 69.14 (q), 58.10 (CH), 48.67 (CH), 47.20 (CH), 47.17 (CH), 31.04 (CH_2), 30.63 (CH_2), 28.34 (CH_2), 26.75 (CH_2), 25.17 (CH_3) and 21.01 (CH_3).

The spectra obtained for all dimers are treated in more detail in the Discussion Section.

8. Isobenzofuran[153]

Reaction of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione with isobenzofuran (generated by FVP from 1,4-epoxy-1,2,3,4-tetrahydronaphthalene using a cold finger trap[154]) produced only polymeric material after 3 h at room temperature. Polymerisation of the isobenzofuran took place in preference to reaction with 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione.

9. Trifluoroacetic acid[148]

7a-Methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (30 mg) was dissolved in trifluoroacetic acid (0.5 cm^3) and the solution monitored over a period of days by ^1H and ^{13}C NMR spectroscopy (using a D_2O capillary and 1 drop of tetramethylsilane for reference purposes). No significant protonation at either of the carbonyl oxygen atoms was observed during this time. See Discussion Section for further discussion of spectra.

10. Deuteriated trifluoroacetic acid[148]

7a-Methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (40 mg) was dissolved in [^2H]trifluoroacetic acid (0.5 cm^3) and monitored over a period of weeks by ^1H NMR spectroscopy. Slow exchange of the proton on C(6) for deuterium was observed,

with a maximum of 83% deuterium incorporation (calculated from NMR integrals) after 4 weeks. Further monitoring showed only decomposition of the compounds present. δ_H [CF_3COOD] 8.19 (1H, s), 3.02 (1H, m), 2.69-2.59 (1H, m), 2.18-1.96 (2H, m) and 1.42 (3H, s); δ_C [CF_3COOD] 194.09 (q), 176.23 (q), 155.50, 71.85 (q), 34.52, 26.80 and 21.15.

11. Methanol

Method (a) - To a solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.04 g, 0.26 mmol) in methanol (8 cm^3) was added a solution of diisopropylethylamine (Hünig's base) (0.034 g, 0.26 mmol) in methanol (2 cm^3). The mixture was stirred at room temperature for 4 min and then the solvent was immediately removed under reduced pressure to give a crude oil which could be purified by Kugelrohr distillation to give cis-*5,6-dihydro-5-methoxy-7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione* **255** (0.039 g, 81%), bp 90 °C (0.2 Torr), (Found: M^+, 183.0902. $C_9H_{13}NO_3$ requires *M*, 183.0895); δ_H 5.33 (1H, dd, ^3J 6.8 and 1.7), 3.35 (3H, s), 2.90-2.61 (2H, m), 2.42-2.24 (2H, m), 2.10-1.96 (2H, m) and 1.41 (3H, s); δ_C 213.76 (q), 177.07 (q), 81.95, 67.73 (q), 55.23, 44.34, 31.42, 30.28 and 23.71; *m/z* 183 (M^+, 6%), 155 (34), 140 (8), 124 (16), 112 (6), 98 (36), 97 (6) and 58 (100).

Method (b) - To a solution of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione (0.4 g, 2.6 mmol) in methanol (15 cm^3) was added a solution of diisopropylethylamine (Hünig's base) (0.68 g, 0.52 mmol) in methanol (5 cm^3). The mixture was heated under reflux for 2 h and then the solvent was removed under reduced pressure to give a crude oil which could be purified by Kugelrohr distillation to give *2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one* **256** (0.484 g, 99%), bp 160 °C

(1.0 Torr), (Found: M^+, 183.0901. $C_9H_{13}NO_3$ requires *M*, 183.0895); δ_H 7.99 (1H, dd, ^3J 3.4 and 4.0), 6.68 (1H, br), 5.07 (1H, dd, ^3J 4.0, ^4J 1.4), 3.60 (3H, s), 2.22-2.13 (2H, m), 1.98-1.90 (2H, m) and 1.24 (3H, s); δ_C 205.22 (q), 173.79 (q), 163.52, 97.88, 65.73 (q), 51.52, 31.46, 28.14 and 22.60; *m/z* 183 (M^+, 50%), 152 (21), 124 (10), 123 (10), 110 (16), 97 (17), 96 (84), 94 (19), 82 (100), 81 (18), 80 (17), 68 (21) and 55 (37).

Method (c) - Reaction of 7a-methyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione with sodium methoxide, for 2 days at room temperature gave an oil after extractive work-up. Examination of the oil by ^1H NMR spectroscopy showed no identifiable products. No starting material was recovered from the reaction.

H. REACTIONS OF 2-METHYL-2-CARBOMETHOXY-ETHYL-1*H*-PYRROL-3(2*H*)-ONE

1. *N*-Bromosuccimide[149]

To a stirred solution of 2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one (0.144 g, 0.8 mmol) in methanol (8 cm^3) was added a solution of *N*-bromo-succinimide (0.138 g, 0.8 mmol) in methanol (2 cm^3). The mixture was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The residue obtained was dissolved in dichloromethane (25 cm^3) and washed with saturated sodium hydrogen carbonate solution (3 x 25 cm^3). The combined aqueous layers were backwashed with dichloromethane (3 x 25 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was then removed under reduced pressure to give a beige solid which was recrystallised to give *4-bromo-2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one* **269** (50%), mp 123-124 °C (from hexane/ethanol), (Found: C, 41.5; H, 4.85; N, 5.65. $C_9H_{12}NO_3Br$ requires C, 41.25; H, 4.6; N, 5.35%); δ_H 8.01 (1H, s), 6.66 (1H, br), 3.59 (3H, s), 2.22-1.91 (4H, m) and 1.27 (3H, s); δ_C 197.97 (q), 173.74 (q), 162.56, 87.98 (q), 66.77 (q), 51.75, 31.65, 28.13 and 22.70; *m/z* 263 (M^+, 10%), 261 (M^+, 9%), 176 (30), 174 (29), 151 (25), 150 (31), 122 (72), 114 (25), 99 (81), 95 (19), 94 (87), 82 (48), 80 (88), 67 (26) and 55 (100).

2. Thiophenol[150]

A solution of 2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one (0.024 g, 0.13 mmol) and thiophenol (0.015 g, 0.13 mmol) in [$^2H_4$]methanol (0.5 cm^3) was placed in an NMR tube and the reaction monitored by ^1H NMR spectroscopy. After 24 h at room temperature no reaction had been observed, with only unreacted starting materials present.

3. Trifluoroacetic acid[148]

2-Methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one (0.03 g) was dissolved in trifluoroacetic acid (0.5 cm^3) and the solution monitored by ^1H NMR spectroscopy (using a D_2O capilliary and 1 drop of tetramethylsilane for reference purposes). Immediate protonation was observed at the carbonyl oxygen atom and the compound gave the following spectra; δ_H [CF_3COOH] 10.24 (1H, br s), 8.72 (1H, br m), 6.04 (1H, m), 3.86 (3H, s), 2.56-2.39 (4H, m) and 1.71 (3H, s); δ_C [CF_3COOH] 196.39 (q), 178.65 (q), 173.93, 100.40, 74.66 (q), 54.94, 31.64, 29.69 and 22.05.

4. Deuteriated trifluoroacetic acid[148]

2-Methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one (0.025 g) was dissolved in [^2H]trifluoroacetic acid (0.5 cm^3) and monitored by ^1H NMR spectroscopy. Exchange of the proton on C(4) for deuterium was observed, with a maximum deuterium incorporation of 94% (calculated from NMR integrals) after 15 min to give compound **270** which gave the following spectrum; δ_H [CF_3COOD] 8.30 (1H, s), 3.43 (3H, s), 2.14-1.97 (4H, m) and 1.29 (3H, s).

5. 5-Methoxymethylidene Meldrum's acid[149]

To a stirred solution of 2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one (0.242 g, 1.3 mmol) in acetonitrile (15 cm^3) was added 5-methoxymethylidene Meldrum's acid (0.246 g, 1.3 mmol). The mixture was stirred at room temperature for 44 h and the solvent was then removed under reduced pressure. The two reaction products were separated by dry flash chromatography using ethyl acetate and *n*-hexane as eluents.

1-(5-Methylidene-2,2-dimethyl-4,6-dioxo-1,3-dioxane)-2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one 271 (37%), mp 158-159 °C (from hexane/ toluene), (Found: C, 56.6; H, 5.45; N, 4.0. $C_{16}H_{19}NO_7$ requires C, 56.95; H, 5.7; N, 4.15%);

δ_H 9.73 (1H, d, ^3J 4.4), 7.89 (1H, s), 5.93 (1H, d, ^3J 4.4), 3.55 (3H, s), 2.27-1.85 (4H, m), 1.70 (6H, s) and 1.42 (3H, s); δ_C 200.62 (q), 171.63 (q), 164.23 (q), 160.72 (q), 158.86, 145.85, 113.24, 104.09 (q), 92.80 (q), 71.22 (q), 51.84, 31.14, 27.55, 27.07 and 22.30; *m/z* 337 (M^+, 1%), 279 (8), 208 (25), 183 (21), 149 (17), 148 (36), 134 (18), 122 (73), 120 (37), 96 (71), 94 (41), 68 (46) and 55 (100).

4-(5-Methylidene-2,2-dimethyl-4,6-dioxo-1,3-dioxane)-2-methyl-2-carbomethoxy-ethyl-1*H*-pyrrol-3(2*H*)-one 272 (19%), bp 85 °C (0.3 Torr), (Found: M^+, 337.1178. $C_{16}H_{19}NO_7$ requires *M*, 337.1162); δ_H 10.13 (1H, d, ^3J 5.1), 9.32 (1H, br), 8.34 (1H, s), 3.56 (3H, s), 2.38-2.00 (4H, m), 1.72 (6H, s) and 1.40 (3H, s); δ_C 200.13 (q), 173.49 (q), 169.52, 164.69 (q), 162.86 (q), 146.28, 108.35 (q), 103.80 (q), 100.87 (q), 67.93 (q), 51.95, 30.91, 28.08, 27.11, 27.06 and 21.61; *m/z* 337 (M^+, 7%), 279 (43), 207 (25), 178 (46), 167 (70), 148 (37), 134 (91), 121 (33), 120 (84), 94 (32), 79 (71), 65 (30) and 55 (100).

6. Pyrolysis of 1-(5-Methylidene-2,2-dimethyl-4,6-dioxo-1,3-dioxane)-2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one

The compound (0.132 g, 0.39 mmol) was pyrolysed (650 °C, 195 °C, 0.02 Torr, 66 min) as described in Section D. The soluble portion of the pyrolysate was then dissolved in solvent to enable removal from the trap and subjected to dry flash column chromatography using *n*-hexane and ethyl acetate as eluents to give two products.

The first was tentatively assigned as the 2,4-disubstituted cyclobutane1,3-dione **273** (6%), (Found: $M^+/2$, 235.0824. $C_{12}H_{13}NO_4$ requires *M/2*, 235.0845); δ_H 7.94 (2H, d, ^3J 4.0), 7.78 (2H, s), 5.71 (2H, d, ^3J 4.0), 3.74 (6H, s), 2.20-1.81 (8H, m) and 1.22 (6H, s); δ_C 202.75 (q), 196.98 (q), 166.82 (q), 158.21, 141.10, 110.38 (q), 107.81, 68.33 (q), 52.34, 39.62, 27.20 and 17.89; *m/z* 235 ($M^+/2$, 37%), 204 (22), 179 (27),

177 (25), 176 (27), 164 (27), 163 (40), 149 (34), 148 (55), 147 (23), 135 (31), 134 (56), 122 (32), 121 (51), 120 (77), 119 (63), 118 (28), 107 (44), 106 (44), 84 (95), 82 (74), 81 (63), 80 (57), 70 (30), 69 (34), 68 (93), 67 (77), 66 (63), 65 (43), 55 (78), 54 (81), 53 (100), 52 (49) and 51 (82).

The second was tentatively assigned as 1-carbomethoxyvinyl-2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one **277** (7%), (Found: M^+, 267.1098. $C_{13}H_{17}NO_5$ requires *M*, 267.1107); δ_H 7.99 (1H, d, ^3J 4.0), 7.35 (1H, d, ^3J 14.3), 5.56 (1H, d, ^3J 4.0), 5.35 (1H, d, ^3J 14.3), 3.68 (3H, s), 3.56 (3H, s), 2.20-1.90 (4H, m) and 1.19 (3H, s); *m/z* 267 (M^+, 28%), 236 (26), 235 (19), 208 (37), 180 (19), 149 (28), 148 (37), 122 (42), 120 (43), 110 (28), 95 (32), 94 (39), 81 (43), 69 (74), 68 (60), 67 (84) and 55 (100).

7. Pyrolysis of 4-(5-Methylidene-2,2-dimethyl-4,6-dioxo-1,3-dioxane)-2-methyl-2-carbomethoxyethyl-1*H*-pyrrol-3(2*H*)-one

The compound (0.05 g, 0.15 mmol) was pyrolysed (650 °C, 195 °C, 0.02 Torr, 48 min) as described in Section D. The soluble portion of the pyrolysate was then dissolved in deuteriated chloroform and examined by ^1H NMR spectroscopy. The spectrum was extremely weak and showed no identifiable peaks.

I. REACTIONS OF 7-HYDROXY-1*H*-PYRROLIZIN-3(2*H*)-ONE

1. Hünig's Base

7-Hydroxy-1*H*-pyrrolizin-3(2*H*)-one (0.04 g, 0.3 mmol) was reacted with Hünig's base (0.038 g, 0.3 mmol) using methanol as solvent. Various reactions at room temperature and heating under reflux, for varying lengths of time failed to give any identifiable products, although there was no evidence of starting material after work-up.

2. *N*-Bromosuccinimide[149]

7-Hydroxy-1*H*-pyrrolizin-3(2*H*)-one (0.03 g, 0.22 mmol) was dissolved in methanol (10 cm^3) and a solution of *N*-bromosuccinimide (0.039 g, 0.22 mmol) in methanol (5 cm^3) was added. The mixture was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. Analysis of the crude solid by ^1H NMR spectroscopy showed only decomposition.

3. Thiophenol[150]

To a stirred solution of 7-hydroxy-1*H*-pyrrolizin-3(2*H*)-one (0.15 g, 1.1 mmol) in methanol (20 cm^3) was added a solution of thiophenol (0.121 g, 1.1 mmol) in methanol (10 cm^3). The mixture was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The crude oil was subjected to dry flash chromatography using ethyl acetate and *n*-hexane as eluents and three products were isolated:

Phenyldisulfide 285, (11%), mp 58-59 °C (lit.,[194] 58-60 °C); δ_H 7.45-7.39 (4H, m) and 7.27-7.10 (6H, m); δ_C 136.88 (q), 128.94, 127.35 and 127.02; *m/z* 218 (M^+,

94%), 185 (22), 184 (12), 154 (31), 110 (33), 109 (100), 108 (16), 86 (83) and 84 (98).

5,6-Dihydro-5-thiophenyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione 286, (9%), bp 75 °C (0.8 Torr), (Found: M^+, 247.0676. $C_{13}H_{13}NO_2S$ requires *M*, 247.0667); δ_H 7.52-7.40 (2H, m), 7.32-7.15 (3H, m), 5.86 (1H, dd, ^3J 8.1 and 1.5), 4.11 (1H, t), 2.96 (1H, ddd, ^2J 19.4, ^3J 8.4, ^4J 0.7), 2.80-2.22 (4H, m) and 1.98-1.87 (1H, m); δ_C 211.03 (q), 175.60 (q), 133.09 (q), 132.13, 129.08, 128.05, 61.34, 57.01, 44.76, 32.61 and 21.81; *m/z* 247 (M^+, 16%), 152 (15), 139 (39), 138 (73), 137 (44), 136 (21), 135 (25), 111 (58), 110 (100), 109 (64), 91 (21), 84 (30), 82 (60), 80 (34) and 77 (36).

5,6-Dihydro-7a-hydroxy-5-thiophenyl-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione 287, (10%), bp 75 °C (0.3 Torr), (Found: M^+, 263.0612. $C_{13}H_{13}NO_3S$ requires *M*, 263.0616); δ_H 8.64 (1H, br s), 7.53-7.40 (2H, m), 7.35-7.19 (3H, m), 5.67 (1H, dd, ^3J 8.1 and 2.2), 3.07 (1H, dd, ^2J 19.4, ^3J 8.1), 2.85 (1H, m) and 2.95-2.00 (4H, m); δ_C 206.74 (q), 175.38 (q), 133.07, 133.27 (q), 129.19, 128.63, 90.59 (q), 55.97, 43.79, 31.29 and 29.42; *m/z* 263 (M^+, 5%), 154 (28), 138 (35), 126 (51), 125 (51), 111 (32), 110 (100), 109 (62), 108 (31), 99 (51), 84 (93) and 69 (99).

4. 5-Methoxymethylidene Meldrum's acid[149]

A mixture of 7-hydroxy-1*H*-pyrrolizin-3(2*H*)-one (0.03 g, 0.22 mmol) and 5-methoxymethylidene Meldrum's acid (0.041 g, 0.22 mmol) was dissolved in [$^2H_3$]acetonitrile (0.5 cm^3) and placed in an NMR tube. The reaction was monitored by ^1H NMR spectroscopy over a period of days (at room temperature), but only unreacted starting material was observed. Heating the reaction mixure to ~75 °C for a number of hours also had no effect.

5. Methylation

Attempts to methylate 7-hydroxy-1*H*-pyrrolizin-3(2*H*)-one at an oxygen atom using a sodium hydride/methyl *p*-toluenesulfonate[102] combination failed, giving only decomposition.

6. Hydrogenation

Hydrogenation of 7-hydroxy-1*H*-pyrrolizin-3(2*H*)-one using 5% palladium on charcoal in a methanol solution at medium pressure (3 atm, 45 p.s.i.) and room temperature gave very inconsistent results. In all cases the double bonds were reduced, but in some molecules the hydroxyl group was left intact, whilst in others it was replaced with a carbonyl group. The mixture of these two compounds was inseparable by dry flash column chromatography; consequently only the ^{13}C spectral data and accurate mass are reported for each compound.

5,6-Dihydro-1*H*-pyrrolizine-3,7(2*H*,7a*H*)-dione[185] **280** (Found: MH^+ (FAB), 140.0716. $C_7H_{10}NO_2$ requires *MH*, 140.0712); δ_C 212.97 (q), 176.52 (q), 63.27, 38.76, 37.44, 32.46 and 22.00. This compound is known[185] but no literature spectra are reported.

5,6,7,7a-Tetrahydro-7-hydroxy-1*H*-pyrrolizin-3(2*H*)-one 279 (Found: MH^+ (FAB), 142.0866. $C_7H_{12}NO_2$ requires *MH*, 142.0868); δ_C 176.36 (q), 68.93, 66.40, 39.12, 35.75, 34.29 and 17.80.

In some cases the 7,7a-dihydroxy, reduced compound **284** was obtained as well as the above products, as the reaction proved to be air sensitive. Attempted separations of mixtures of products by dry flash column chromatography proved unsuccessful. This reaction is treated in more detail in the Discussion Section.

J. PREPARATION OF PRODIGIOSIN ANALOGUES

1. Preparation of the A-B Ring System - Method 1

(a) 2,2-Dimethyl-5-[1,1-bis(methylsulfanyl)methylidene]-1,3-dioxane-4,6-dione preparation[96]

To a well stirred solution of Meldrum's acid (21.0 g, 0.15 mol) in DMSO (75 cm^3) was added triethylamine (42.0 cm^3, 0.3 mol) and carbon disulfide (9.0 cm^3, 0.15 mol) in quick succession. The mixture was then stirred vigorously for 1 h at room temperature before being cooled in an ice bath. Iodomethane (19.5 cm^3, 0.3 mol) was then added slowly to the ice-cooled reaction mixture. When addition was complete the mixture was allowed to warm to room temperature and was stirred for 4 h. Ice water (120 cm^3) was then added with scratching to precipitate the product **96**, which was filtered off and washed with a light petroleum/tetrahydrofuran mixture (2:1 respectively); the material obtained at this point was pure enough for subsequent reactions (16.8 g, 46%), mp 118-119 °C (lit.,[186] 119-121 °C); δ_H 2.60 (6H, s) and 1.70 (6H, s).

(b) 2,2-Dimethyl-5-{[1-methylsulfanyl-1-(2-thienyl)]methylidene}-1,3-dioxane-4,6-dione preparation[96]

The Grignard reagent, 2-thienylmagnesium bromide was prepared in the usual manner (in freshly distilled dry tetrahydrofuran) from magnesium turnings (2 g) and 2-bromothiophene (9.78 g, 60 mmol).

To a well stirred solution of 2,2-dimethyl-5-[1,1-bis(methylsulfanyl)methylidene]-1,3-dioxane-4,6-dione (4.96 g, 20 mmol) in dry tetrahydrofuran (50 cm^3), under a nitrogen atmosphere was added a solution of 2-thienylmagnesium bromide (60 mmol) in dry tetrahydrofuran (50 cm^3) dropwise over a period of 20 min. The

mixture was stirred for a further 1 h under nitrogen. Hydrochloric acid (6M, 60 cm^3) was added to the reaction mixture to hydrolyse the addition product. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 50 cm^3). The combined organic layers were then washed with water (3 x 100 cm^3) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the crude product **290** which was recrystallised (3.91 g, 69%), mp 224-226 °C (dec.) [lit.,[96] 225-227 °C (dec.)]; δ_H ([$^2H_6$]DMSO) 7.85 (1H, m), 7.17 (2H, m), 2.11 (3H, s) and 1.73 (6H, s).

(c) Preparation of 3-hydroxy-5-(2-thienyl)-thiophene[96]

2,2-Dimethyl-5-[(1-methylsulfanyl-2-thienyl)methylidene]-1,3-dioxane-4,6-dione (2.0 g, 7 mmol) was pyrolysed (625 °C, 180 °C, 0.01 Torr, 4.5 h) as described in Section D. The product **291** was obtained as a crystalline solid and was scraped from the trap and purified by recrystallisation (1.20 g, 94%), mp 113-114 °C (from ethanol) (lit.,[96] 113-115 °C); δ_H ([$^2H_6$]DMSO) 9.71 (1H, br s), 7.43 (1H, dd, ^3J 5.1, ^4J 1.1), 7.22 (1H, dd, ^3J 3.6, ^4J 1.1), 7.04 (1H, dd, ^3J 5.1 and 3.6), 6.85 (1H, d, ^4J 1.6) and 6.22 (1H, d, ^4J 1.6).

(d) Preparation of 3-methoxy-5-(2-thienyl)-thiophene[102]

To a stirred suspension of sodium hydride (80% dispersion in oil, 0.288 g, ~6 mmol, washed three times with *n*-hexane and dried at 0.1 Torr) in dimethylimidazolidinone (20 cm^3) was added a solution of 3-hydroxy-5-(2-thienyl)-thiophene (0.346 g, 2 mmol) in dimethylimidazolidinone (5 cm^3) under a stream of nitrogen. A solution of methyl *p*-toluenesulfonate (0.372 g, 2 mmol) in dimethylimidazolidinone (4 cm^3) was then added dropwise and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then quenched in ethanol/water (40 cm^3, 1:1) and extracted with ether (3 x 50 cm^3). The combined organic layers were

back-extracted with water (5 x 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the desired product **292** (0.267 g, 68%), bp 140°C (0.4 Torr) [lit.,[163] 122-124 °C (0.2 Torr)]; δ_H 7.19 (1H, dd, ^3J 5.1, ^4J 1.2), 7.14 (1H, dd, ^3J 3.6, ^4J 1.2), 6.98 (1H, dd, ^3J 5.1 and 3.6), 6.82 (1H, d, ^4J 1.7), 6.12 (1H, d, ^4J 1.7) and 3.79 (3H, s).

(e) Preparation of 2-formyl-3-methoxy-5-(2-thienyl)-thiophene[163]

Phosphoryl chloride (13.2 cm^3) was added to dimethylformamide (100 cm^3), followed by a solution of 3-methoxy-5-(2-thienyl)-thiophene (2.59 g, 0.013 mol) in dimethylformamide (25 cm^3). The reaction mixture was heated at 40 °C for 1.5 h and then added carefully to water (100 cm^3). Sodium hydroxide (2M, 150 cm^3) was then added with stirring and the resulting solution extracted with ether (4 x 100 cm^3). The combined organic layers were then washed with water (2 x 200 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product **288** which was recrystallised (2.44 g, 82%), mp 106-107 °C (from ethanol) (lit.,[163] 106.5-108.5 °C); δ_H 9.93 (1H, s), 7.34 (2H, m), 7.05 (1H, dd, ^3J 3.7 and 5.0), 6.89 (1H, s) and 4.00 (3H, s).

2. Attempted Preparation of the A-B Ring System - Method 2

(a) Preparation of 5-dimethylaminomethylidene-4-methoxypyrrol-2(2*H*)-one[187]

1,5-Dihydro-4-methoxypyrrol-2(2*H*)-one (0.452 g, 4 mmol) was dissolved in dimethylformamide dimethylacetal (15 cm^3) and the mixture heated under reflux for 5 days. The solvent was then removed under pressure and the residue subjected to dry flash column chromatography using *n*-hexane, ethyl acetate and methanol as eluents to give the title compound **318** (0.450 g, 67%), mp 153-154 °C (dec.) (from hexane/toluene), (Found: C, 57.25; H, 7.05; N, 16.7. $C_8H_{12}N_2O_2$ requires C, 57.15; H, 7.2; N, 16.65%); δ_H 9.49 (1H, br), 6.14 (1H, s), 4.89 (1H, d, ^4J 1.1), 3.71 (3H, s) and 3.02 (6H, s); δ_C 171.12 (q), 166.93 (q), 125.04, 106.23 (q), 86.42, 57.34 and 42.29 (2 x C); *m/z* 168 (M^+, 36%), 125 (10), 113 (60), 98 (15), 86 (33), 85 (23), 84 (100) and 69 (93).

(b) Reaction of 5-dimethylaminomethylidene-4-methoxypyrrol-2(2*H*)-one with pyrrole[174]

To a solution of phosphoryl chloride (0.767 g, 5 mmol) in dichloroethane (3 cm^3) was added dropwise, with stirring, a solution of 5-dimethylaminomethylidene-4-methoxypyrrol-2(2*H*)-one (0.084 g, 0.5 mmol) in dichloroethane (3 cm^3). The mixture was stirred at room temperature for 30 min and a solution of pyrrole (0.034 g, 0.5 mmol) in dichloroethane (2 cm^3) was then added. The mixture was stirred for a further 1 h at room temperature. Aqueous sodium acetate solution (5M, 30 cm^3) was then added and the mixture extracted with chloroform (3 x 30 cm^3). The combined organic layers were washed with pH4 buffer solution (2 x 50 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The black solid residue obtained was very insoluble. ^1H NMR spectroscopy of the minor soluble portion (in [$^2H_6$]DMSO) showed no identifiable peaks.

3. Preparation of the B-Ring

(a) 2-Formyl-3-methoxypyrrole preparation[165]

To a solution of copper sulfate pentahydrate (37.45 g, 0.15 mol) in deionised water (600 cm^3) was added 4-methoxypyridine-*N*-oxide (2.147 g, 0.015 mol). The mixture was degassed for 30 min and then irradiated for 6 h using a 400 W mercury lamp. During irradiation a gentle stream of nitrogen was maintained through the solution. Sodium chloride (180 g) was added to the reaction mixture with stirring, and then the solution was continuously extracted with dichloromethane overnight. The organic layer was separated and dried thoroughly ($MgSO_4$) and the solvent was removed under reduced pressure. The crude brown oil obtained was subjected to dry flash chromatography using *n*-hexane and ethyl acetate as eluents to give the desired compound as a pale yellow solid **311** (0.196 g, 11%), mp 134-135 °C (from toluene) (lit.,[188] 135-136 °C); δ_H 10.47 (1H, br), 6.99 (1H, m), 5.84 (1H, m) and 3.85 (3H, s).

4. Preparation of C-Rings

(a) 2-Methyl-3-pentylpyrrole

(i) 4-Pentylpyridine preparation[166,167]

To a flask (equipped with a dry ice condenser) containing liquid ammonia (~180 cm^3) was added sodium metal (7.5 g, 0.31 mol) portionwise, with stirring. The mixture was stirred for 30 min (until the reaction turned from blue to grey in colour) and then 4-methylpyridine (27.93 g, 0.3 mol) was added rapidly with vigorous stirring. Ice-cold 1-bromobutane (41.1 g, 0.3 mol) was then added (less rapidly) and the mixture was stirred for a further 3 h allowing the ammonia to evaporate. Water (300 cm^3) was added and the mixture was extracted with ether (4 x 150 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give an orange oil, which was purified by distillation (using a Vigreux column) to give the desired product **300** (39.0 g, 89%), bp 46-48 °C (0.5 Torr) [lit.,[189] 62-65 °C (2.0 Torr)]; δ_H 8.42-8.33 (2H, m), 7.03-6.92 (2H, m), 2.47 (2H, t, ^3J 7.7), 1.60-1.44 (2H, m), 1.35-1.18 (4H, m) and 0.79 (3H, t, ^3J 6.8); δ_C 151.32 (q), 149.26, 123.51, 34.82, 30.98, 29.62, 22.09 and 13.59; *m/z* 149 (M^+, 31%), 106 (12), 93 (100), 92 (10) and 73 (14).

(ii) 4-Pentylpyridine-*N*-oxide preparation[168]

To a solution of 4-pentylpyridine (19.5 g, 0.131 mol) in glacial acetic acid (85 cm^3) was added hydrogen peroxide (27.5% solution, 16.0 cm^3). The mixture was heated, with stirring, at 75 °C for 4 h and then cooled to room temperature before a further addition of hydrogen peroxide (27.5% solution, 16.0 cm^3). The mixture was heated for a further 48 h at 75 °C and then concentrated to ~30 cm^3 (using a high vacuum, keeping the water bath below 40 °C and taking the relevant safety precautions).

Water (30 cm^3) was then added, the mixture again concentrated to ~30 cm^3 (again taking the necessary precautions) and then dissolved in chloroform (90 cm^3). The solution was added to a potassium carbonate paste (100 g K_2CO_3 in 100 ml water) with stirring, the mixture was filtered and the organic layer of the filtrate was separated and dried ($MgSO_4$). The solvent was then removed under reduced pressure to give the desired product as a pale brown oil **301** (20.17 g, 93%), bp 105 °C (0.30 Torr), (Found: M^+, 165.1158. $C_{10}H_{15}NO$ requires *M*, 165.1154); δ_H 7.98-7.86 (2H, m), 6.94-6.81 (2H, m), 2.37 (2H, t, ^3J 7.7), 1.44-1.32 (2H, m), 1.18-0.99 (4H, m) and 0.65 (3H, t, ^3J 6.6); δ_C 148.92 (q), 138.11, 125.46, 33.70, 30.53, 29.24, 21.77 and 13.35; *m/z* 165 (M^+, 30%), 109 (24), 108 (100), 93 (46), 92 (24), 91 (17) and 65 (17).

(iii) 2-Formyl-3-pentylpyrrole preparation[165]

To a solution of copper sulfate pentahydrate (7.49 g, 0.03 mol) in deionised water (600 cm^3) was added 4-pentylpyridine-*N*-oxide (0.5 g, 3 mmol). The mixture was degassed for 30 min and then irradiated for 6 h using a 400 W mercury lamp. During irradiation a gentle stream of nitrogen was maintained through the solution. Sodium chloride (150 g) was added to the reaction mixture with stirring, and then the solution was continuously extracted with dichloromethane overnight. The organic layer was separated and dried thoroughly ($MgSO_4$) and the solvent was removed under reduced pressure. The crude brown oil obtained was subjected to dry flash chromatography using *n*-hexane and ethyl acetate as eluents to give the desired compound as a cream solid **302** (0.099 g, 20%), bp 150-155 °C (0.30 Torr), (Found: M^+, 165.1158. $C_{10}H_{15}NO$ requires *M*, 165.1154); δ_H 9.81 (1H, br), 9.61 (1H, s), 7.03 (1H, t, ^3J 2.5), 6.15 (1H, t, ^3J 2.5), 2.75 (2H, t, ^3J 7.6), 1.61 (2H, m), 1.47-1.28 (4H, m) and 0.90 (3H, t, ^3J 6.8); δ_C 177.44, 138.31 (q), 129.05 (q), 126.00, 111.40, 31.35, 31.26, 25.13, 22.32 and 13.86; *m/z* 165 (M^+, 23%), 122 (42), 109 (23), 108 (35), 86 (64), 84 (100) and 80 (31).

(iv) 2-Methyl-3-pentylpyrrole preparation[169]

To a stirred mixture of crushed potassium hydroxide pellets (0.28 g) and hydrazine hydrate (0.21 cm^3) in ethylene glycol (2.8 cm^3) was added 2-formyl-3-pentylpyrrole (0.232 g, 1.4 mmol). The mixture was heated under reflux for 15 min and then allowed to cool to room temperature. Water (20 cm^3) was added and the solution was extracted with ether (3 x 30 cm^3). The combined organic layers were back-washed with water (5 x 30 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give the desired product as a brown oil **9** (0.049 g, 23%), bp 60 °C (0.5 Torr) [lit.,[16] 119 °C (15 Torr)]; δ_H 7.82 (1H, br), 6.60 (1H, m), 6.04 (1H, m), 2.41 (2H, t, ^3J 7.6), 2.20 (3H, s), 1.63-1.50 (2H, m), 1.48-1.30 (4H, m) and 0.93 (3H, t, ^3J 7.0).

(b) 2-Undecylpyrrole[26]

The Grignard reagent, ethylmagnesium bromide, was prepared in the usual manner in freshly distilled dry ether (20 cm^3) from magnesium turnings (1.4 g) and bromoethane (5.44 g, 0.05 mol).

The Grignard reagent was cooled to 0 °C and a solution of freshly distilled pyrrole (3.36 g, 0.05 mol) in dry ether (5 cm^3) was added dropwise with stirring. The mixture was heated under reflux for 30 min. A solution of 1-bromoundecane (11.8 g, 0.05 mol) in dry ether (10 cm^3) was then added dropwise and the mixture was heated under reflux for a further 24 h (still under an atmosphere of nitrogen). The mixture was allowed to cool to room temperature and saturated ammonium chloride solution (50 cm^3) was added to decompose the magnesium salts. The two layers that formed were separated and the aqueous layer was extracted with ether (2 x 50 cm^3). The combined organic layers were washed with water (2 x 50 cm^3), saturated sodium chloride solution (1 x 50 cm^3) and then dried ($MgSO_4$). The solvent was removed

under reduced pressure and acetone (15 cm^3) was added to the brown, oily residue. The mixture was cooled in ice and the precipitate formed was removed by filtration. The solvent was removed from the filtrate to give a dark brown oil which was distilled to give the desired product **11**, which crystallised on standing (0.77 g, 7%), mp 42-43 °C (from acetone) (lit.,[26] 42-43 °C); δ_H 7.89 (1H, br), 6.67 (1H, m), 6.15 (1H, m), 5.93 (1H, m), 2.61 (2H, t, ^3J 7.7), 1.68-1.54 (2H, m), 1.39-1.20 (16H, m) and 0.91 (3H, t, ^3J 6.5); δ_C 132.76 (q), 115.82, 108.08, 104.69, 31.80, 29.55, 29.52, 29.47, 29.40, 29.34, 29.28, 29.23, 27.60, 22.57 and 14.00; *m/z* 221 (M^+, 10%), 94 (16), 81 (33) and 80 (100).

(c) 3-Ethyl-1,2,4-trimethylpyrrole[171]

Dimethyl sulfoxide (10 cm^3, dried over sodium hydroxide pellets) was added to crushed potassium hydroxide pellets (1.12 g, 0.02 mol) and the mixture was stirred for 5 min at room temperature. 2,4-Dimethyl-3-ethylpyrrole (0.616 g, 0.005 mol) was added and the resulting mixture was stirred for a further 45 min. The reaction was cooled in ice and iodomethane (1.42 g, 0.01 mol) was added dropwise with stirring. The mixture was again stirred for 45 min at room temperature. Water (10 cm^3) was added and the mixture was extracted with ether (3 x 50 cm^3). The combined organics were washed with water (3 x 25 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product which was purified by Kugelrohr distillation (the receiver bulb cooled with dry ice throughout) **305** (0.418 g, 61%), bp 75 °C (0.2 Torr); δ_H[190] 6.32 (1H, s), 3.47 (3H, s), 2.42 (2H, q, ^3J 7.3), 2.14 (3H, s), 2.05 (3H, d, ^4J 0.7), 1.10 (3H, t, ^3J 7.3); δ_C 127.13 (q), 124.34 (q), 120.66 (q), 117.48, 33.05, 17.67, 15.72, 9.80 and 9.26.

(d) 2-Aminopyridinium picrate[191]

2-Aminopyridine (0.941 g, 10 mmol) was dissolved in the minimum amount of acetone. Picric acid (wet with ethanol, 4.58 g, ~20 mmol) was dissolved in the minimum amount of acetone and the 2-aminopyridine solution added to it, causing immediate precipitation to occur. Ether (200 cm^3) was added and when precipitation was complete the solid was collected by filtration and recrystallised from ethanol to give the desired product as a bright yellow crystalline solid (2.863 g, 89%), mp 223-224 °C (from ethanol) (lit.,[192] 224-225°C); δ_H ([$^2H_6$]DMSO) 8.68 (1H, s), 8.57 (1H, s), 8.02-7.88 (4H, m) and 7.14-6.93 (2H, m); δ_C ([$^2H_6$]DMSO) 161.26 (q), 154.21 (q, 2 x C), 144.17, 141.74 (q), 136.01, 125.75 (2 x C), 125.16 (q), 113.65 and 112.24.

5. Preparation of the A-B-C Ring System

(a) Method 1[170]

2-Formyl-3-methoxy-5-(2-thienyl)-thiophene (0.045 g, 0.2 mmol) and the appropriate C-ring compound (0.2 mmol) were dissolved in *n*-pentane (3 cm^3) containing the minimum amount of dichloromethane required for solubility. The solution was then cooled to 0 °C and phosphoryl chloride (0.031 g, 0.2 mmol) was added with stirring over 1 min. The reaction mixture was stirred at room temperature for the time quoted and then either the solid purple product was collected by filtration, or the solvent was removed under reduced pressure from the purple solution to give the desired product as a thick oil (which was characterised by high resolution mass spectrometry). The following salts were prepared in this way. The reaction time and C-Ring compound used are given in brackets for each example.

3,5-Dimethyl-4-ethyl-2-[3-methoxy-5-(2-thienyl)-thienyl-2-methylidene]-2*H*-pyrrolium dichlorophosphate 85a (5 min, 2,4-dimethyl-3-ethylpyrrole), (70%), mp 179-180 °C (dec.) (from ethanol) [lit.,[163] 180 °C (dec.)]; δ_H 13.01 (1H, br s), 7.92 (1H, d, ^3J 3.8), 7.66 (1H, s), 7.45 (1H, d, ^3J 5.0), 7.10 (1H, dd, ^3J 5.0 and 3.8), 6.93 (1H, s), 4.12 (3H, s), 2.75 (3H, s), 2.26 (3H, s), 2.41 (2H, q, ^3J 7.5) and 1.07 (3H, t, ^3J 7.5).

4-Pentyl-5-methyl-2-[3-methoxy-5-(2-thienyl)-thienyl-2-methylidene]-2*H*-pyrrolium dichlorophosphate 303 (30 min, 2-methyl-3-pentylpyrrole), (77%), (Found: M^+ (cation), 358.1330. $C_{20}H_{24}NOS_2$ requires *M*, 358.1299); δ_H 14.15 (1H, br), 8.13 (1H, s), 7.61-7.48 (2H, m), 7.18-7.07 (3H, m), 4.15 (3H, s), 2.45 (3H, s), 2.39 (2H, t, ^3J 7.7), 1.60-1.48 (3H, m), 1.44-1.29 (3H, m) and 0.91 (3H, t, ^3J 6.4); δ_C 170.11 (q), 158.64 (q), 152.97 (q), 138.96 (q), 135.42 (q), 132.90 (q), 130.49, 130.27, 129.06, 128.61, 125.51, 116.25 (q), 111.17, 60.12, 31.32, 28.77, 25.95, 22.26, 13.87

and 13.29; *m/z* (FAB) 358 (M^+ (cation), 100%), 357 (53), 343 (30), 328 (27), 286 (44), 209 (37), 206 (58), 196 (10), 184 (24), 150 (58) and 90 (19).

5-Undecyl-2-[3-methoxy-5-(2-thienyl)-thienyl-2-methylidene]-2*H*-pyrrolium dichlorophosphate 304 (15 min, 2-undecylpyrrole), (97%), (Found: M^+ (cation), 428.2095. $C_{25}H_{34}NOS_2$ requires *M*, 428.20819); δ_H 13.67 (1H, br), 8.40 (1H, s), 7.60-7.52 (2H, m), 7.52 (1H, m), 7.17 (1H, m), 6.99 (1H, s), 6.62 (1H, m), 4.16 (3H, s), 2.86 (2H, t, ^3J 7.7), 1.75 (2H, m), 1.38-1.16 (16H, m) and 0.86 (3H, t, ^3J 6.6); δ_C 171.92 (q), 161.49 (q), 156.34 (q), 135.11 (q), 132.73 (q), 132.45, 131.85, 129.80, 129.44, 128.84, 121.64, 117.11 (q), 110.74, 60.49, 31.73, 29.43, 29.39, 29.31, 29.25, 29.17, 29.08, 28.84, 27.79, 22.51 and 13.97; *m/z* (FAB) 428 (M^+ (cation), 63%), 427 (56), 370 (28), 312 (26), 300 (35), 287 (46), 286 (30), 272 (55), 268 (30), 234 (27), 209 (100), 178 (24), 169 (24) and 149 (30).

4-Ethyl-1,3,5-trimethyl-2-[3-methoxy-5-(2-thienyl)-thienyl-2-methylidene]-2*H*-pyrrolium dichlorophosphate 306 (15 min, 3-ethyl-1,2,4-trimethyl-pyrrole), (93%), (Found: M^+ (cation), 344.1122. $C_{19}H_{22}NOS_2$ requires *M*, 344.1143); δ_H 8.13 (1H, br), 7.65 (1H, br), 7.53 (1H, m), 7.14 (2H, m), 4.20 (3H, s), 3.87 (3H, br s), 2.69-2.44 (8H, m) and 1.06 (3H, t, ^3J 7.7); δ_C 170.48 (q), 158.00 (q), 154.04 (q), 145.10 (q), 135.14 (q), 133.97 (q), 131.37 (q), 130.86, 130.14, 129.35, 125.94, 114.04 (q), 110.77, 60.73, 30.81, 17.61, 14.14, 13.97 and 13.17; *m/z* (FAB) 344 (M^+ (cation), 5%), 343 (12), 278 (5), 255 (8), 237 (11), 236 (20), 196 (18), 169 (11), 153 (14), 152 (13), 137 (14), 111 (26), 97 (47), 96 (36), 83 (53), 69 (61) and 43 (100).

3-Methoxy-2-[3-methoxy-5-(2-thienyl)-thienyl-2-methylidene]-2*H*-thiophenium dichlorophosphate 308 (15 min, 3-methoxythiophene), (84%), (Found: M^+ (cation), 321.0068. $C_{15}H_{13}S_2O_3$ requires *M*, 321.0078); δ_H ([$^2H_6$]Acetone) 7.79 (1H, s), 7.36 (1H, m), 7.18 (2H, m), 7.09 (1H, s), 6.92 (1H, d), 7.04 (1H, dd), 3.78 (3H, s) and 3.71 (3H, s); *m/z* (FAB) 321 (M^+ (cation), 50%), 315 (100), 261 (57), 239 (49), 209 (54), 207 (28), 171 (35), 147 (47), 145 (47), 127 (41) and 69(50).

(b) Method 2

To a solution of 2-formyl-3-methoxy-5-(2-thienyl)-thiophene (0.135 g, 0.6 mmol) in isopropanol (25 cm^3) was added 3-aminopyrazole (0.051 g, 0.6 mmol). The mixture was heated under reflux for 24 h and the solvent was removed under reduced pressure to give the crude product which was recrystallised to give *3-[*N*-(3-methoxy-5-(2-thienyl)-thienyl-2-methylidene)]-aminopyrazole* **310** (0.109 g, 63%), mp 130-131 °C (from hexane/ethyl acetate), (Found: C, 54.2; H, 4.05; N, 14.35. $C_{13}H_{11}N_3OS_2$ requires C, 53.95; H, 3.85; N, 14.5%); δ_H ([$^2H_6$]DMSO) 12.63 (1H, br), 8.84 (1H, s), 7.63 (2H, m), 7.51 (1H, m), 7.37 (1H, s), 7.15 (1H, m), 6.32 (1H, m) and 3.99 (3H, s); δ_C ([$^2H_6$]DMSO) 161.04 (q), 158.25(q), 148.83, 139.63 (q, br), 136.51, 130.44 (q, br), 128.87, 127.51, 125.78, 117.38 (q), 113.53, 96.48 (br) and 59.20; *m/z* 289 (M^+, 100%), 260 (14), 258 (22), 209 (14), 208 (17), 207 (88), 179 (27), 135 (14), 108 (19) and 94 (20).

This method was also tried with 2-aminopyridine and 2-aminopyridinium picrate, but in both cases only unreacted starting material was recovered, even after extended reflux times.

6. Preparation of B-C Ring Systems

(a) Preparation of 3,5-dimethyl-4-ethyl-2-(3-methoxypyrrolyl-2-methylidene)-2*H*-pyrrolium dichlorophosphate[170]

2-Formyl-3-methoxypyrrole (0.037 g, 0.3 mmol) and 2,4-dimethyl-3-ethylpyrrole (0.3 mmol) were dissolved in *n*-pentane (3 cm^3) containing the minimum amount of dichloromethane required for solubility. The solution was then cooled to 0 °C and phosphoryl chloride (0.046 g, 0.6 mmol) added with stirring over 1 min. The reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure from the purple solution to give the desired product **316** (0.094 g, 86%), (Found: M^+ (cation), 231.1505. $C_{14}H_{19}N_2O$ requires *M*, 231.1497); δ_H 11.76 (2H, br), 7.53 (1H, br s), 7.24 (1H, s), 5.97 (1H, s), 3.96 (3H, s), 2.46 (3H, s), 2.44 (2H, q), 2.24 (3H, s) and 1.05 (3H, t, ^3J 7.4); δ_C 165.02 (q), 154.45 (q), 143.33 (q), 139.72, 131.13 (q), 126.60 (q), 118.31, 117.59 (q), 96.24, 58.84, 17.02, 14.10, 12.67 and 9.85; *m/z* (FAB) 231 (M^+ (cation), 100%), 230 (55), 229 (25), 216 (35), 215 (22), 202 (29), 201 (23), 199 (28), 170 (16), 146 (17), 132 (19), 120 (21) and 70 (14).

(b) Preparation of 3,5-dimethyl-4-ethyl-2-(3-methoxypyrrolyl-2-methylidene)-2*H*-pyrrole

3,5-Dimethyl-4-ethyl-2-(3-methoxypyrrolyl-2-methylidene)-2*H*-pyrrolium dichlorophosphate (0.109 g, 0.3 mmol, prepared as above) was dissolved in dichloromethane (30 cm^3) and extracted with sodium hydroxide solution (2M, 3 x 30 cm^3). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the desired product (0.055 g, 80%), bp 220 °C (1.0 Torr), (Found: M^+, 230.1428. $C_{14}H_{18}N_2O$ requires *M*, 230.1419); δ_H 13.46 (1H, br), 7.53 (1H, br), 7.23 (1H, m), 5.85 (1H, m), 3.92 (3H, s), 2.56 (3H, s), 2.38 (2H, q, ^3J 7.6), 2.22 (3H,

s) and 1.03 (3H, t, ^3J 7.6); δ_C 164.24 (q), 155.37 (q), 142.16 (q), 138.99, 130.90 (q), 126.60 (q), 118.28, 117.31 (q), 95.22, 58.44, 17.06, 14.15, 12.70 and 9.74; *m/z* 230 (M^+, 29%), 199 (27), 155 (31), 149 (49), 141 (40), 136 (29), 123 (32), 111 (40), 109 (35), 97 (67), 95 (55), 84 (56), 83 (40), 81 (78), 73 (56), 71 (71) and 69 (100).

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Synthesis of 2-Substituted 1,3-Oxazin-6-ones by Gas-phase Pyrolysis

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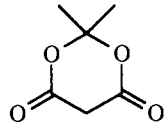
Key words: Oxazinones: flash vacuum pyrolysis; Meldrum's acid; ^{13}C NMR spectroscopy; ketene intermediates

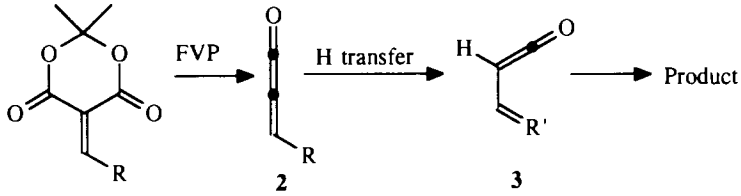
Abstract: *Acylaminomethylene Meldrum's acid derivatives* **5** *are prepared either by direct reaction of methoxymethylene Meldrum's acid* **4** *with primary amides, or by acylation of aminomethylene Meldrum's acid* **6**. *Pyrolysis of the substrates* **5** *under FVP conditions gives the title compounds* **8** *in good yields.*

In recent years we have been studying transformations of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **1**[1] derivatives into other heterocyclic ring systems using pyrolytic methodology.



1

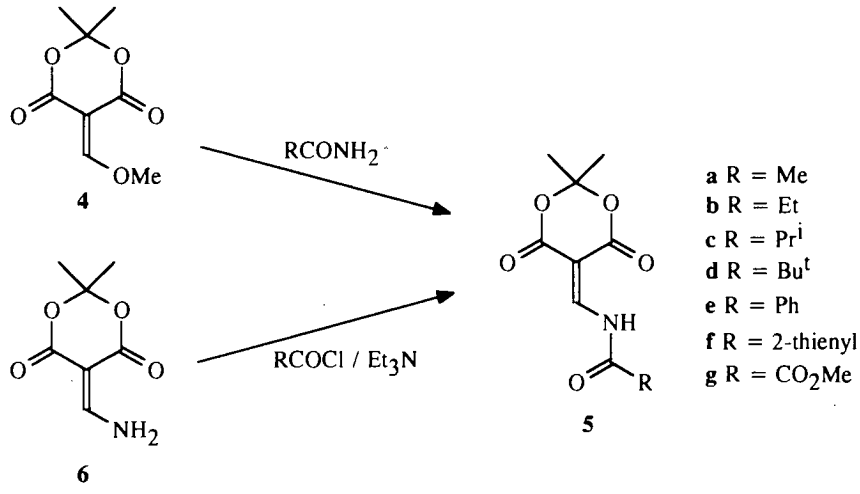
The strategy has involved the design of appropriate substrates so that hydrogen transfer in the key methyleneketene intermediate **2** (first identified by Brown and co-workers[2]) leads to a conjugated ketene **3** which collapses to give the product (Scheme 1).



Scheme 1

In this way, we have synthesised a range of monocyclic (pyridazin-3-ones,[3] 3-hydroxypyrroles,[4] 3-hydroxythiophenes,[5] azepin-3(2*H*)-ones[6] *etc.*) and bicyclic (pyrrolizin-3-ones[7] and their aza-analogues,[8] pyrazolo[1,2*a*]1,2,3-triazinium-4-olate[9] *etc.*) heterocyclic systems, generally in good yield and in preparatively useful quantities. Here we present an extension of this work which has led to the first general route to 2-substituted 1,3-oxazin-6-ones, which themselves are important substrates in heterocycle transformations.[10]

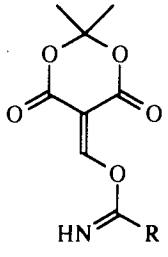
Methoxymethylene Meldrum's acid **4** is a very reactive electrophilic reagent for both nitrogen[4] and carbon nucleophiles.[11] We have now found that even primary amides react as *N*-nucleophiles with this reagent to give the acylamino derivatives **5** (Scheme 2), though extended reaction times (up to 96 h) in refluxing acetonitrile may be required (see Experimental section). Aliphatic, aromatic and heterocyclic amides can be used, but although the products could be isolated without chromatography, the yields are only moderate (*ca.* 50%). The reaction of formamide itself with **4** is still under investigation, but the room temperature NMR spectrum of the product indicates that exchange processes are taking place in this compound which are not found with the other examples. Some amides were poorly soluble under the standard conditions which resulted in very low yields. However, the synthesis of these products could be improved by direct acylation of aminomethylene Meldrum's acid **6** using the appropriate acyl chloride in the presence of triethylamine in refluxing acetonitrile (Scheme 2). In this way, the yield of **5c** was improved from 24% to 70% and this is the method of choice for more complex acylamino derivatives such as the carbomethoxy compound **5g**. Yamamoto and co-workers were unable to *N*-acylate aminomethylene Meldrum's acid derivatives substituted at the methine carbon atom,[12] which may represent a limitation of this route.



Scheme 2

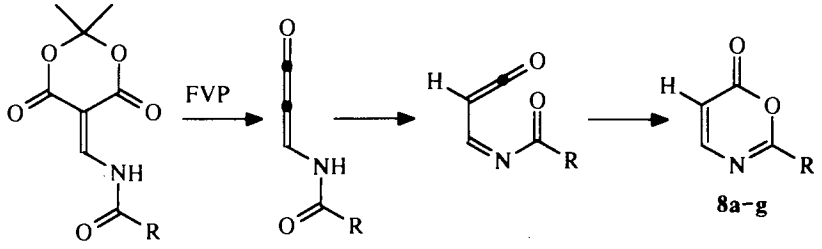
The products **5** were characterised by their ^{1}H NMR spectra which showed typical coupling constants of ^3J 12-13 Hz from the exocyclic methine position to the *N*-*H*. This confirms that the amide is acting as an *N*-nucleophile, since the most likely alternative product **7** would not show such a three bond

coupling. The size of the coupling constant also confirms that the configuration about the C-N single bond is *s-trans*, as expected from the potential hydrogen bonding with the ring carbonyl group. In agreement with this, both ring carbonyl groups give distinct peaks in the ^{13}C NMR spectra. These assignments have been further confirmed by X-ray crystallography.[13] All the derivatives **5** show significant molecular ions in their electron impact mass spectra, with loss of *m/z* 57 or 58 [corresponding to (acetone - H) or acetone] as the initial breakdown peak.[14] Loss of carbon dioxide or of alkyl substituents compete for the later fragmentations.



7

Flash vacuum pyrolysis (FVP) of the Meldrum's acid derivatives **5a-g** at 500-550 °C and 0.01 Torr gave the 2-substituted 1,3-oxazin-6-ones **8a-g** in 62-80% yield (Scheme 3). The method is compatible with primary, secondary and tertiary substituents at the 2-position (**8a-d**) as well as aromatic (**8e**), heterocyclic (**8f**) and functional (**8g**) substituents. Although 2-aryl oxazinones have been previously prepared,[15] earlier methods have been shown to fail for 2-alkyl substituents. The present method is therefore the first route to 2-alkyloxazinones, as well as being applicable to other substituents.



5a-g

a R = Me
b R = Et
c R = Pr^i
d R = Bu^t
e R = Ph
f R = 2-thienyl
g R = CO_2Me

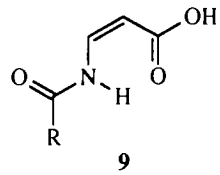
Scheme 3

2,4-Disubstituted oxazinones have been made previously by liquid-phase thermolysis of appropriately substituted Meldrum's acid derivatives,[12] (either in solution or in the melt) but the yields and

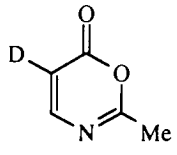
reaction conditions were dependent on the substitution pattern. We therefore believe that the gas-phase method reported here is more reliable and generally applicable.

The characterisation of the products **8** follows from comparison of their ^{1}H NMR spectra with that of the unsubstituted compound previously reported.[16] Thus the protons at the 4- and 5-positions resonate at δ_H 7.5-7.8 and 6.0-6.2 (^3J *ca.* 6.8 Hz) respectively [*c.f.* δ_H 7.78 and 6.38 (^3J 7.2 Hz)[16] reported for the parent compound]. Stájer *et al.* quote a coupling constant of ^3J 6.8 Hz for a range of 2-aryl-1,3-oxazinones.[17] The mass spectra of the oxazinones **8** generally show relatively weak molecular ions with characteristic loss of *m/z* 28 (CO). In addition, most have significant peaks at *m/z* 96 due to loss of the 2-substituent.

As found for the parent 1,3-oxazin-6-one,[16] alkyl-substituted compounds **8** are susceptible to slow hydrolysis in [^{2}H]chloroform solution to give the open-chain products **9**, which were identified by their characteristic enamide protons at *ca.* δ_H 5.1 (^3J *ca.* 9 Hz) and 7.5 (^3J *ca.* 9 and 11.5 Hz) in the ^{1}H NMR spectra. After 2 weeks in solution in [^{2}H]chloroform at room temperature the methyl derivative **9a** (R = Me) was formed to the extent of 12%. In contrast, the 2-thienyl derivative **8f** was apparently stable in solution over a period of 8 weeks.



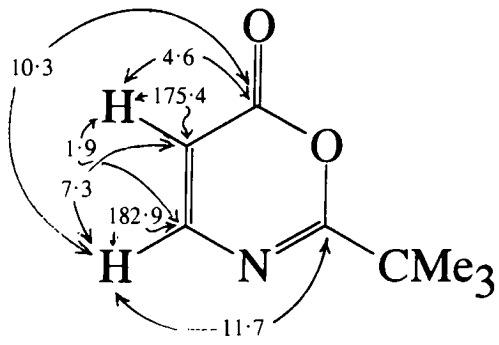
9



8a'

Formation of the oxazin-6-ones presumably follows from the mechanism in Scheme 1, with the final step being the electrocyclisation of an acyliminoketene intermediate (Scheme 3). We have established the hydrogen transfer step leading to the acyliminoketene by a deuterium labelling experiment; exchange of the *N-H* of **5a** with deuterium was accomplished by heating in [^{2}H] methanol, and immediate pyrolysis after removal of solvent gave the oxazin-6-one **8a'** specifically labelled in the 5-position, as shown by the absence of the signal at δ_H 6.0, in agreement with the proposed mechanism.

The ^{13}C NMR spectra of some 2-aryloxazinones have been reported,[17] and our data are in agreement with the previous work (see Experimental section). The t-butyl derivative **8d** was used to determine the major proton-carbon coupling parameters as follows. C(5) (109.31 p.p.m.) and C(4) (153.89 p.p.m.) appeared as doublets of doublets due to one bond (175.4 and 182.9 Hz respectively) and two bond (7.3 and 1.9 Hz respectively) couplings. The quaternary C(6) (158.80 p.p.m.) also showed two couplings (10.3 and 4.6 Hz); examination of the ^{1}H coupled spectrum of the deuterium labelled compound **8a'** showed that the major interaction to be a three bond coupling with the proton on C(4). The other quaternary C(2) is complex due to coupling with the substituent, but again **8a'** enabled assignment of one significant interaction (^3J 11.7 Hz) with H(4). These data are summarised in the Figure.



Figure

EXPERIMENTAL

^1H NMR spectra were recorded at 200 or 250 MHz, and ^{13}C NMR spectra at 50 or 63 MHz for solutions in [^2H]chloroform unless otherwise stated. Quaternary signals in the ^{13}C NMR spectra are indicated (q).

5-N-(AMIDO)METHYLENE-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

Method 1

To a well stirred solution of 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione **4** (1.86g, 10 mmol) in acetonitrile (50 ml) was added the amide (10 mmol). The mixture was heated under reflux for the time quoted, and the solvent was removed under reduced pressure to give the crude product which could be recrystallised.

The following 5-*N*-(amido)methylene-2,2-dimethyl-1,3-dioxane-4,6-diones **5** were prepared. The reflux time for each example is given in brackets.

5-*N*-(Acetamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5a (24h), (62%), m.p. 138-140 °C (from ethanol), (Found: C, 50.75; H, 5.35; N, 6.55. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.55%); δ_H 10.94 (1H, broad d), 8.70 (1H, d, ^3J 12.5 Hz), 2.27 (3H, s) and 1.64 (6H, s); δ_C 168.06(q), 163.81(q), 161.62(q), 149.76, 105.35(q), 93.13(q), 26.98 and 23.48; *m/z* 213 (M^+, 26%), 198(14), 171(28), 160(23), 156(54), 155(15), 114(52), 111(24), 51(15) and 57(100).

5-*N*-(Propionamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5b (24h), (58%), m.p. 141-142 °C (from ethanol), (Found: C, 52.8; H, 5.8; N, 6.05. $C_{10}H_{13}NO_5$ requires C, 52.85; H, 5.75; N, 6.15%); δ_H 10.94 (1H, broad d), 8.72 (1H, d, ^3J 12.8 Hz), 2.51 (2H, q, ^3J 7.4 Hz), 1.62 (6H, s) and 1.13 (3H, t, ^3J 7.4 Hz); δ_C 171.68(q), 163.86(q), 161.62(q), 159.76, 105.24(q), 92.90(q), 29.70, 26.91 and 7.93; *m/z* 227 (M^+, 27%), 170(37), 169(41), 141(18), 140(28), 125(17), 114(54), 69(20) and 57(100).

5-*N*-(iso-Butyramido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5c (48h), (24%), m.p. 100-102 °C (from ethanol), (Found: C, 54.45; H, 5.9; N, 5.7. $C_{11}H_{15}NO_5$ requires C, 54.75; H, 6.25; N, 5.8%); δ_H 11.12 (1H, broad d), 8.80 (1H, d, ^3J 12.7 Hz), 2.66 (1H, septet, ^3J 6.9 Hz), 1.68 (6H, s) and 1.22 (6H, d, ^3J 6.9 Hz); δ_C 174.70(q), 164.24(q), 161.68(q), 150.27, 105.45(q), 93.29(q), 35.77, 27.09 and 18.33; *m/z* 241 (M^+, 8%), 184(9), 183(8), 140(18), 114(20), 96(10), 71(45), 70(20) and 43(100).

5-*N*-(Trimethylacetamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5d (72h), (48%), m.p. 99-100 °C (from ethanol), (Found: C, 56.1; H, 7.05; N, 5.45. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5%); δ_H 11.46 (1H, broad d), 8.79 (1H, d, ^3J 12.6 Hz), 1.67 (6H, s) and 1.25 (9H, s); δ_C 176.27(q), 164.48(q), 161.62(q), 150.71, 105.45(q), 93.40(q), 39.58(q), 27.09 and 26.44; *m/z* 255 (M^+, 4%), 198(13), 140(12), 114(8), 85(11), 69(10), 59(11) and 57(100).

5-*N*-(Benzamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5e (48h), (48%), m.p. 153-154 °C (from ethanol), (Found: C, 61.0; H, 4.85; N, 4.95. $C_{14}H_{13}NO_5$ requires C, 61.1; H, 4.75; N, 5.1%); δ_H 12.08 (1H, broad d), 9.02 (1H, d, ^3J 12.4 Hz), 7.94 (2H, m), 7.58 (3H, m) and 1.72 (6H, s); δ_C 164.56(q), 163.62(q), 161.48(q), 150.62, 134.15, 129.92(q), 129.04, 128.01, 105.54(q), 94.03(q) and 27.06; *m/z* 275 (M^+, 3%), 218(3), 173(2), 106(8), 105(100), 77(42) and 51(15).

5-*N*-(Thienyl-2-carboxamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5f (96h), (51%), m.p. 121-122 °C (from ethanol), (Found: C, 51.0; H, 4.0; N, 5.25. $C_{12}H_{11}NO_5S$ requires C, 51.25; H, 3.9; N, 5.0%); δ_H ([$^2H_6$] DMSO) 11.71 (1H, broad d), 8.65 (1H, d, ^3J 12.5 Hz), 8.16 (1H, dd, ^3J 4.8 Hz, ^4J 1.0 Hz), 7.92 (1H, dd, ^3J 3.8 Hz, ^4J 1.0 Hz), 7.33 (1H, dd, ^3J 4.8 and 3.8 Hz) and 1.71 (6H, s); δ_C ([$^2H_6$] DMSO) 163.84(q), 161.74(q), 158.54(q), 149.59, 136.85, 134.79(q), 133.22, 129.40, 105.73(q), 93.97(q) and 26.87; *m/z* 281 (M^+, 18%), 224(10), 223(18), 111(100) and 83(7).

Method 2

To a well stirred solution of 5-aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione[18] **6** (1.71g, 10 mmol) and triethylamine (10 mmol) in acetonitrile (90 ml) was added the acid chloride (10 mmol) in acetonitrile (10 ml) dropwise over a period of 10 min. The mixture was heated under reflux for the time quoted, and the solvent was then removed under reduced pressure. The crude product was redissolved in dichloromethane. and the solution was washed with water (3 x 50 ml) and dilute HCl (2M, 1 x 50 ml). The combined aqueous washings were back extracted with dichloromethane (2 x 50 ml). The combined organic layers were then dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product which could then be recrystallised.

The following 5-*N*-(amido)methylene-2,2-dimethyl-1,3-dioxane-4,6-diones **5** were prepared. The precursor acid chloride and reflux time for each example are given in parentheses.

5-*N*-(iso-Butyramido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5c (isobutyryl chloride, 2h), (70%), m.p. 100-101 °C (from ethanol). Spectra obtained were identical with those reported above.

5-*N*-(2-Carbomethoxyamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 5g (methyl oxalyl chloride, 8h), (56%), m.p. 136-137 °C (from ethanol), (Found: C, 46.9; H, 4.7; N, 5.75. $C_{10}H_{11}NO_7$ requires C, 46.7; H, 4.3; N, 5.45%); δ_H 12.08 (1H, broad d), 8.70 (1H, d, ^3J 12.7 Hz), 3.98 (3H, s) and 1.71 (6H, s); δ_C 163.21(q), 161.02(q), 158.03(q), 154.42(q), 147.78, 105.98(q), 97.32(q), 54.47 and 27.30; *m/z* 257 (M^+, 3%), 200(31), 198(26), 140(80), 114(54), 96(17), 70(27) and 69(100).

2-SUBSTITUTED-6H-1,3-OXAZIN-6-ONES 8

The amidomethylene Meldrum's acid derivative **5** was sublimed or distilled at low pressure through an empty silica furnace tube (2.5 x 35 cm) maintained at 500-550 °C, and products were collected in a liquid nitrogen trap. Involatile solid products which condensed at the exit point of the furnace were

scraped from the trap, whereas volatile solids and liquids were washed from the trap with solvent. After the solvent had been removed under reduced pressure, the crude pyrolysate was purified by either recrystallisation or bulb-to-bulb distillation. The following 2-substituted 6*H*-1,3-oxazin-6-ones **8** were prepared by pyrolysis; the amidomethylene Meldrum's acid precursor **5** and pyrolysis conditions (furnace temperature, inlet temperature, average pressure, pyrolysis time and amount of substrate) are given for each example in parentheses.

2-Methyl-6*H*-1,3-oxazin-6-one 8a [5-*N*-(acetamido-) **5a**, 500 °C, 150 °C, 0.01 Torr, 22 min, 0.5 g], (77%), b.p. 35-40 °C (0.15 Torr), (Found: M^+, 111.0321. $C_5H_5NO_2$ requires M, 111.0320); δ_H 7.55 (1H, d, ^3J 6.8 Hz), 6.09 (1H, d, ^3J 6.8 Hz) and 2.36 (3H, s); δ_C 168.31(q), 158.39(q), 153.83, 109.39 and 21.46; *m/z* 111 (M^+, 31%), 96(19), 86(38), 84(48), 83(32), 69(17), 49(29) and 43(100).

2-Ethyl-6*H*-1,3-oxazin-6-one 8b [5-*N*-(propionamido-) **5b**, 500 °C, 160 °C, 0.01 Torr, 37 min, 0.5 g], (62%), b.p. 40-45 °C (0.20 Torr), (Found: M^+, 125.0473. $C_6H_7NO_2$ requires M, 125.0477); δ_H 7.53 (1H, d, ^3J 6.8 Hz), 6.03 (1H, d, ^3J 6.8 Hz), 2.54 (2H, q, ^3J 7.5 Hz) and 1.16 (3H, t, ^3J 7.5 Hz); δ_C 171.79(q), 158.23(q), 153.58, 109.23, 27.89 and 9.49; *m/z* 125 (M^+, 36%), 97(11), 96(75), 87(12), 70(26), 69(11) and 57(100).

2-iso-Propyl-6*H*-1,3-oxazin-6-one 8c [5-*N*-(iso-butyramido-) **5c**, 550 °C, 165 °C, 0.01 Torr, 31 min, 0.5 g], (68%), b.p. 40-45 °C (0.40 Torr), (Found: M^+, 139.0638. $C_7H_9NO_2$ requires M, 139.0633); δ_H 7.58 (1H, d, ^3J 6.9 Hz), 6.06 (1H, d, ^3J 6.9 Hz), 2.79 (1H, septet, ^3J 7.0 Hz) and 2.22 (6H, d, ^3J 7.0 Hz); δ_C 174.80(q), 158.53(q), 153.82, 109.35, 34.03 and 19.21; *m/z* 139 (M^+, 11%), 121(9), 119(10), 96(47), 88(22), 86(74), 84(100) and 71(11).

2-t-Butyl-6*H*-1,3-oxazin-6-one 8d [5-*N*-(trimethylacetamido-) **5d**, 550 °C, 135 °C, 0.02 Torr, 25 min, 0.5 g], (70%), b.p. 45-50 °C (0.40 Torr), (Found: M^+, 153.0783. $C_8H_{11}NO_2$ requires M, 153.0790); δ_H 7.64 (1H, d, ^3J 6.8 Hz), 6.10 (1H, d, ^3J 6.8 Hz) and 1.32 (9H, s); δ_C 176.70(q), 158.80(q), 153.89, 109.31, 38.23(q) and 27.45; *m/z* 153 (M^+, 15%), 138(8), 125(6), 110(9), 96(45), 84(7), 70(14), 69(9) and 57(100).

2-Phenyl-6*H*-1,3-oxazin-6-one 8e [5-*N*-(benzamido-) **5e**, 550 °C, 150 °C, 0.01 Torr, 77 min, 0.5 g], (79%), m.p. 85-87 °C (from hexane/toluene), (lit.,[15] 85-87 °C); δ_H 8.19 (2H, m), 7.78 (1H, d, ^3J 6.7 Hz), 7.47 (3H, m) and 6.18 (1H, d, ^3J 6.7 Hz); δ_C 164.46(q), 158.08(q), 154.44, 133.24, 129.34(q), 128.62, 128.31 and 109.28; *m/z* 173 (M^+, 10%), 146(8), 106(8), 105(100), 77(42) and 58(25).

2-(2-Thienyl)-6*H*-1,3-oxazin-6-one 8f [5-*N*-(thienyl-2-carboxamido-) **5f**, 550 °C, 180 °C, 0.01 Torr, 52 min, 0.5 g], (72%), m.p. 109-110 °C (from ethanol), (Found: C, 53.4; H, 2.85; N, 7.9. $C_8H_5NO_2S$ requires C, 53.6; H, 2.8; N, 7.8%); δ_H 7.91 (1H, dd, ^3J 3.8 Hz, ^4J 1.2 Hz), 7.71 (1H, d, ^3J 6.8 Hz), 7.63 (1H, dd, ^3J 5.0 Hz, ^4J 1.2 Hz), 7.14 (1H, dd, ^3J 5.0 and 3.8 Hz) and 6.10 (1H, d, ^3J 6.8 Hz); δ_C 160.98(q), 157.60(q), 154.75, 133.74, 133.34(q), 132.76, 128.52 and 108.36; *m/z* 179 (M^+, 59%), 151(27), 127(19), 113(13), 112(18), 111(100), 83(22) and 57(14).

2-Carbomethoxy-6*H*-1,3-oxazin-6-one 8g [5-*N*-(2-carbomethoxyamido-) **5g**, 500 °C, 225 °C, 0.01 Torr, 37 min, 0.5 g], (80%), m.p. 93-95 °C [after distillation at 155 °C (0.5 Torr)], (Found: C, 46.25; H, 3.65; N, 9.1. $C_6H_5NO_4$ requires C, 46.45; H, 3.25; N, 9.05%); δ_H ([$^2H_6$] DMSO) 7.98 (1H, d, ^3J 6.8 Hz), 6.66 (1H, d, ^3J 6.8 Hz) and 3.88 (3H, s); δ_C ([$^2H_6$] DMSO) 157.66(q), 157.02(q), 153.69,

153.53(q), 114.50 and 53.75; *m/z* 155 (M^+, 3%), 154(10), 128(17), 114(10), 96(100), 95(28), 70(13), 69(12) and 59(10).

2-Methyl-5-[^{2}H]-6*H*-1,3-oxazin-6-one 8a' (*c.f.* ref 19) 5-*N*-(Acetamido)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione **5a** (0.21 g, 1 mmol) was dissolved in deuteriated methanol (CH_3OD, 10 ml) by heating. The solution was allowed to stand for 15 min and the solvent was then removed under reduced pressure at the oil pump. The crude deuteriated solid was immediately pyrolysed (inlet tube flame dried, 500 °C, 150 °C, 0.02 Torr, 12 min). The product was extracted with deuteriated chloroform and shown by NMR spectroscopy to be the desired 2-methyl-5-[^{2}H]-6*H*-1,3-oxazin-6-one, with 93% deuterium incorporation. Spectra are reported in the Discussion section.

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Table 2. *Selected geometric parameters (Å, °)*

O1—C1	1.260 (5)	C1—C2	1.520 (5)
O2—C1	1.236 (5)	C2—C5	1.526 (6)
N1—C2	1.480 (5)	C3—C4	1.494 (7)
N1—C3	1.504 (6)	C4—C5	1.510 (6)
C2—N1—C3	107.8 (3)	N1—C2—C5	104.7 (3)
O2—C1—O1	125.9 (4)	C1—C2—C5	113.2 (3)
O2—C1—C2	117.8 (4)	C4—C3—N1	101.4 (3)
O1—C1—C2	116.4 (3)	C3—C4—C5	103.7 (3)
N1—C2—C1	111.4 (3)	C4—C5—C2	105.5 (4)
C3—N1—C2—C1	106.7 (3)	C2—N1—C3—C4	35.7 (4)
C3—N1—C2—C5	−16.1 (4)	N1—C3—C4—C5	−40.8 (4)
O2—C1—C2—N1	179.3 (3)	C3—C4—C5—C2	32.0 (4)
O1—C1—C2—N1	−1.9 (4)	N1—C2—C5—C4	−9.8 (4)
O2—C1—C2—C5	−63.0 (5)	C1—C2—C5—C4	−131.4 (3)
O1—C1—C2—C5	115.8 (4)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H11···O1^{i}	0.900	1.841	2.723 (4)	165.7 (2)
N1—H1···O1	0.900	2.153	2.632 (4)	112.5 (2)
O3—H311···O2	0.996	1.833	2.815 (4)	168.3 (2)
O3—H312···O3^{ii}	0.886	2.158	2.889 (5)	139.4 (3)
O3—H313···O3^{iii}	0.902	2.035	2.902 (6)	160.7 (2)
N1—H1···O3^{iv}	0.900	2.581	3.243 (5)	130.9 (2)

Symmetry codes: (i) $x, y, z-1$; (ii) $1-x, y, 2-z$; (iii) $1-x, y, 1-z$; (iv) $\frac{1}{2}-x, \frac{1}{2}+y, 1-z$.

All H atoms were located in difference Fourier maps and were not refined.

Data collection: Stoe AED diffractometer software. Cell refinement: Stoe AED diffractometer software. Data reduction: Stoe AED diffractometer software. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1971) and *SCHAKAL*92 (Keller, 1992). Software used to prepare material for publication: *SHELXL*93.

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Acta Cryst. (1997). C**53**, 1956–1958

An Extended Imide Containing Two Methylene Meldrum's Acid Units

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Abstract

We report the crystal structure of the unusual imide 5,5′-(iminodimethylidene)bis(2,2-dimethyl-1,3-dioxane-4,6-dione), $C_{14}H_{15}NO_8$, which contains two Meldrum's acid (dioxanedione) substituents. The geometry of the imide moiety shows the effects of delocalization of the N-atom

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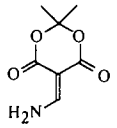
lone pair, while the overall conformation of the molecule is associated with the formation of strong intramolecular hydrogen bonds.

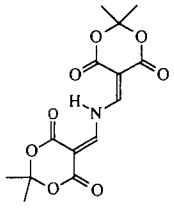
Comment

As a continuation of our work on the reactions of aminomethylene Meldrum's acid, (1), with acid chlorides (McNab & Withell, 1996), we investigated its reaction with oxalyl chloride, (2). Surprisingly, the only significant product after 20 h under reflux in MeCN was the extended imide (3) (18%), and we now report the characterization of this compound by X-ray crystallography.



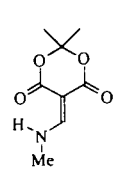
(1)

(2)

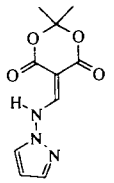


(3)

Compound (3) shows an *sE* configuration about both N1—C7 and N1—C7′, allowing intramolecular bifurcated hydrogen bonding of N1—H with O6 and O6′. Delocalization of the N1 lone pair through two methylenedioxanedione systems is reflected in the much longer N1—C7/7′ bond lengths [average 1.362 (8) Å] compared with those of the aminomethylenedioxanedione model compounds (4) (Blake, Hunter & McNab, 1989) [1.281 (14) Å] and (5) (Blake, Gould, Irving, McNab & Morrow, 1994) [1.315 (2) Å]. The average C5/5′—C7/7′ distance [1.350 (9) Å] in (3) shows correspondingly more double-bond character than in both (4) [1.409 (15) Å] and (5) [1.373 (2) Å], but the effect is much smaller and less significant. The average C4/4′—C5/5′ bond length [1.465 (9) Å] is slightly longer than the average C5/5′—C6/6′ bond length [1.451 (9) Å], and although this distinction is of borderline significance in (3), a similar consistent effect is seen in the model compounds (4) and (5), which may be taken to imply a resonance contribution to the hydrogen bonding in these systems. The average C6/6′—C5/5′—C7/7′ bond angle [121.6 (7)°] is larger than C4/4′—C5/5′—C7/7′ [117.3 (7)°] in order to accommodate the hydrogen bond. In general, the bond angles in (3) are very similar to those in (4) and (5).



(4)



(5)

The conformations of the dioxanedione rings in (3) can both be described as being approximately 30% chair and 70% boat (Gould, Taylor & Thorpe, 1995). With the exception of the atoms C2 and C2′ and their methyl substituents, the molecule is essentially planar, with the largest deviation from the mean plane being that of O4′ (0.211 Å).

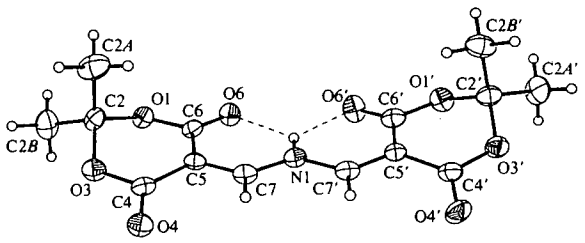
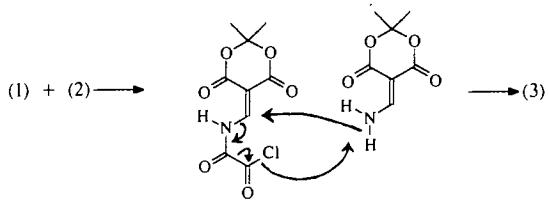


Fig. 1. A view of the molecule with the atom-numbering scheme. Displacement ellipsoids enclose 30% probability surfaces. H atoms have been assigned arbitrary radii.

The reasons for the unexpected formation of (3) remain unclear, but it may be significant that much longer reaction times are required than for related reactions (McNab & Withell, 1996). The oxalyl chloride plays a significant role in the process since if (1) is heated for 20 h in MeCN in the presence of triethylamine and in the absence of oxalyl chloride, the starting material (1) is quantitatively recovered. The mechanism shown in the scheme below is consistent with these observations.



Experimental

A solution of oxalyl chloride (1.26 g, 10 mmol) in acetonitrile (10 ml) was added dropwise to a stirred solution of (1) (1.71 g, 10 mmol) and triethylamine (2.04 g, 20 mmol) in acetonitrile (40 ml) over a period of 10 min. The mixture was heated under reflux for 20 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (100 ml) and extracted with water (2 × 100 ml). A further portion of water (100 ml) was added and the gelatinous mixture was filtered through celite. The organic layer was separated, washed with dilute hydrochloric acid (1 *M*, 50 ml) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give (3) (0.30 g, 18%), m.p. 501 K (dec.) (from acetonitrile). Elemental analysis found C 51.4, H 5.05, N 4.25%; $C_{14}H_{15}NO_8$ requires C 51.7, H 4.55, N 4.3%. NMR: δ_H ($CDCl_3$) 12.80 (1H, *t*, ^3J = 12.6 Hz), 8.84 (2H, *d*, ^3J = 12.6 Hz) and 1.70 p.p.m. (12H, *s*); δ_C ($CDCl_3$) 162.65 (*q*), 161.34 (*q*), 156.33, 105.66 (*q*), 96.40 (*q*) and 26.95 p.p.m. *m/z*

(EI): 325 (M^+, 19%), 268 (12), 267 (75), 210 (22), 209 (42), 181 (20), 165 (20), 153 (63), 137 (28) and 121 (47).

Crystal data

$C_{14}H_{15}NO_8$
M_r = 325.27
Triclinic
$P\bar{1}$
a = 5.191 (4) Å
b = 11.627 (6) Å
c = 12.998 (7) Å
α = 75.80 (4)°
β = 79.33 (6)°
γ = 88.49 (6)°
V = 747.2 (8) Å^3
Z = 2
D_x = 1.446 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 22 reflections
θ = 9.5–12.0°
μ = 0.120 mm^{-1}
T = 298 (2) K
Lath
0.31 × 0.12 × 0.04 mm
Pale yellow

Data collection

Stoe Stadi-4 diffractometer
ω–2θ scans
Absorption correction: none
2607 measured reflections
1954 independent reflections
734 reflections with $I > 2\sigma(I)$
R_{int} = 0.188

θ_{max} = 22.5°
$h = -5 \rightarrow 5$
$k = -11 \rightarrow 12$
$l = 0 \rightarrow 13$
3 standard reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.065
$wR(F^2)$ = 0.113
S = 0.980
1946 reflections
209 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0204P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002

$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0091 (13)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å)*

O1—C6	1.354 (7)	O1′—C6′	1.361 (8)
O1—C2	1.442 (7)	O1′—C2′	1.438 (8)
C2—O3	1.455 (8)	C2′—O3′	1.433 (8)
O3—C4	1.357 (7)	O3′—C4′	1.359 (8)
C4—O4	1.202 (7)	C4′—O4′	1.209 (8)
C4—C5	1.466 (9)	C4′—C5′	1.463 (9)
C5—C7	1.352 (9)	C5′—C7′	1.347 (9)
C5—C6	1.447 (8)	C5′—C6′	1.454 (9)
C6—O6	1.209 (7)	C6′—O6′	1.211 (8)
C7—N1	1.351 (8)	N1—C7′	1.373 (8)
O6···O6′	3.178 (7)		

The crystal diffracted only weakly at higher angles and accordingly data were collected to only $2\theta_{max}$ = 45°, resulting in a low data-to-parameter ratio. The high value of R_{int} reflects the distribution of equivalents over rather weak high-angle data.

Data collection: *DIF*4 (Stoe & Cie, 1990*a*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1990*b*). Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL* (Sheldrick, 1995).

We thank EPSRC for provision of a four-circle diffractometer and postgraduate funding for KW, and Lonza Ltd for a gift of Meldrum's acid.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: MU1340). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). C**53**, 1958–1960

1,3-Di(ethoxy-ethoxy-methoxy)calix[4]-arene†

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(*Received 21 June 1996; accepted 14 May 1997*)

Abstract

In the solid state, the title compound, $C_{38}H_{44}O_8$, adopts a cone conformation, which is somewhat distorted. The cone conformation is also observed by NMR spectroscopy in solution. The distortion consists of a

† Alternative name: 26,28-bis(3,6-dioxaheptyloxy)pentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,-19(26),21,23-dodecaene-25,27-diol.

Acta Cryst. (1998). C**54**, 234–236

Two Methylsulfanylmethylene Derivatives of Meldrum's Acid

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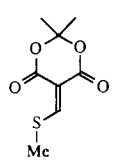
Abstract

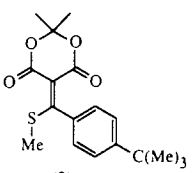
Functionalization of methylsulfanylmethylene Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) with aryl or thienyl substituents, to give 5-[(*p*-*tert*-butylphenyl)(methylsulfanyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione, $C_{18}H_{22}O_4S$, and 2,2-dimethyl-5-[(methylsulfanyl)(2-thienyl)methylene]-1,3-dioxane-4,6-dione, $C_{12}H_{12}O_4S_2$, results in a lengthening of the C—S single bond and the adoption of essentially a boat conformation by the Meldrum's acid heterocycle.

Comment

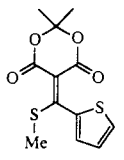
We have previously published the crystal structure of methylsulfanylmethylene Meldrum's acid, (1) (Blake *et al.*, 1989), and as part of a continuing study on the effects of substitution on the structural chemistry of Meldrum's acid derivatives, we report here the effect of the replacement of the methylene H atom with an aryl group, (2), and with a 2-thienyl group, (3). This latter substituent exhibits twofold rotational disorder and so, in this case, our comments are restricted to the remainder of the molecule.



(1)



(2)



(3)

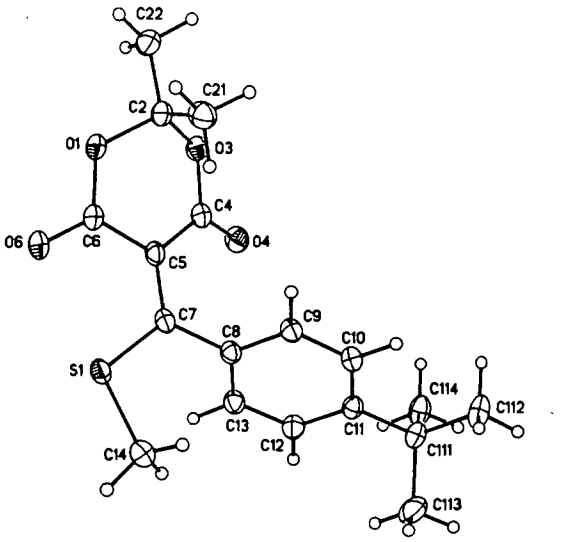


Fig. 1. A view of (2) with the atom-numbering scheme. Displacement ellipsoids enclose 30% probability surfaces.

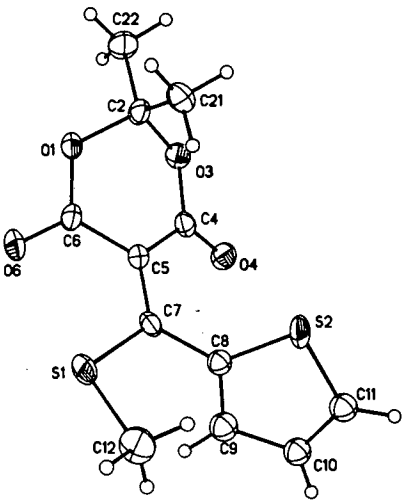


Fig. 2. A view of (3) with the atom-numbering scheme. Displacement ellipsoids enclose 30% probability surfaces. The minor disorder component is not shown.

The S1—C7 bond lengths in (2) and (3) [1.738 (1) and 1.744 (4) Å, respectively] are significantly longer than the corresponding distance in (1) [1.694 (3) Å], and this may reflect the electron donation by the additional ring into the methylenedioxanedione unit. There appears to be a consistent trend towards a more single-bond character in the C5—C7 bonds of (2) and (3) [1.368 (2) and 1.377 (5) Å, respectively] than in (1) [1.356 (4) Å]. The dioxanedione ring in (3) has local mirror symmetry to within experimental error, but in (2), C4—C5 is significantly longer [1.485 (2) Å] than C5—C6 [1.467 (2) Å].

There is a substantial difference between the angle at the S atom in (1) [100.94 (16)°] and the related angles at S1 in (2) and (3) [104.94 (7) and 104.1 (2)°, respectively], which may be due to steric interaction with the additional phenyl or thiophene rings. Similarly, the angle C5—C7—S1 is much smaller in (2) [120.3 (1)°] and (3) [121.2 (3)°] than in (1) [126.16 (3)°], as is the angle C4—C5—C6 [116.4 (1) and 115.6 (3)° in (2) and (3),

compared with 120.2 (3)° in (1)]. Whereas the dioxanedione ring systems in (2) and (3) can be described as being mainly in a boat conformation (16% chair, 1% twist boat, 83% boat in both cases; Gould *et al.*, 1995), in (1), the O1—C6—C5—C4—O3 moiety is effectively planar, the ring being 31% chair, 1% twist boat and 68% boat. Qualitatively expressed, a second substituent on C7 apparently induces a distortion of the dioxanedione ring, which forces C7 and the O4 and O6 carbonyl groups in opposite directions with respect to the best O1—C6—C5—C4—O3 plane. The plane of the aryl ring in (2) lies at 114.2 (1)° with respect to the S1—C7—C8 plane, which itself makes an angle of only 9.4 (1)° with the C4—C5—C6 plane; the corresponding parameters for (3) are 114.1 (2) and 5.6 (3)°, respectively.

Experimental

Compounds (2) and (3) were prepared according to the procedures described by Hunter & McNab (1995). Crystals of (2) were grown by slow evaporation of an acetone solution, while those of (3) were grown by sublimation.

Compound (2)

Crystal data

$C_{18}H_{22}O_4S$
M_r = 334.43
Triclinic
$P\bar{1}$
a = 9.4818 (9) Å
b = 9.7365 (14) Å
c = 10.6089 (10) Å
α = 93.469 (8)°
β = 113.697 (5)°
γ = 97.890 (8)°
V = 881.08 (16) Å^3
Z = 2
D_x = 1.26 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 60 reflections
θ = 20–22°
μ = 1.73 mm^{-1}
T = 220.0 (2) K
Block
0.43 × 0.39 × 0.23 mm
Orange

Data collection

Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device (Cosier & Glazer, 1986)
ω–θ scans with on-line profile fitting (Clegg, 1981)
Absorption correction: ψ scans (North *et al.*, 1968)
T_{min} = 0.405, T_{max} = 0.673
7548 measured reflections
3123 independent reflections
2785 reflections with $I > 2\sigma(I)$
R_{int} = 0.014
θ_{max} = 70.17°
$h = -11 \rightarrow 11$
$k = -11 \rightarrow 11$
$l = -7 \rightarrow 12$
3 standard reflections
frequency: 60 min
intensity decay: 1.0%

Refinement

Refinement on F
R = 0.0338
wR = 0.0402
S = 1.1073
2785 reflections
209 parameters
H atoms placed geometrically after each cycle
Weighting: Chebychev polynomial (Carruthers & Watkin, 1979)
$(\Delta/\sigma)_{max}$ = 0.005
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 50 (3)
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 1. *Selected geometric parameters (Å, °) for (2)*

S1—C7	1.738 (1)	O4—C4	1.200 (2)
S1—C14	1.801 (2)	C4—C5	1.485 (2)
O1—C2	1.444 (2)	C5—C6	1.467 (2)
O1—C6	1.353 (2)	C5—C7	1.368 (2)
C2—O3	1.436 (2)	O6—C6	1.204 (2)
O3—C4	1.353 (2)	C7—C8	1.488 (2)
C7—S1—C14	104.94 (7)	S1—C7—C5	120.3 (1)
C4—C5—C6	116.4 (1)	S1—C7—C8	118.4 (1)
C4—C5—C7	121.6 (1)	C5—C7—C8	121.3 (1)
C6—C5—C7	121.8 (1)		

Compound (3)

Crystal data

$C_{12}H_{12}O_4S_2$
M_r = 284.34
Triclinic
$P\bar{1}$
a = 6.137 (8) Å
b = 7.170 (8) Å
c = 15.00 (3) Å
α = 79.00 (8)°
β = 84.36 (11)°
γ = 83.08 (8)°
V = 641.2 (15) Å^3
Z = 2
D_x = 1.473 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 50 reflections
θ = 9.5–16.0°
μ = 0.418 mm^{-1}
T = 150.0 (2) K
Block
0.55 × 0.55 × 0.40 mm
Colourless

Data collection

Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device (Cosier & Glazer, 1986)
ω–2θ scans
Absorption correction: none
3309 measured reflections
2200 independent reflections
2068 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 25.09°
$h = -7 \rightarrow 7$
$k = -8 \rightarrow 8$
$l = 0 \rightarrow 17$
3 standard reflections
frequency: 60 min
intensity decay: 4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.187
S = 1.152
2200 reflections
166 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0945P)^2 + 1.3847P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.49 e Å^{-3}
$\Delta\rho_{min}$ = −0.72 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 2. *Selected geometric parameters (Å, °) for (3)*

O1—C6	1.365 (5)	C5—C7	1.377 (5)
O1—C2	1.443 (5)	C5—C6	1.472 (5)
C2—O3	1.435 (4)	C6—O6	1.207 (5)
O3—C4	1.355 (4)	C7—C8	1.473 (5)
C4—O4	1.223 (4)	C7—S1	1.744 (4)
C4—C5	1.472 (5)	S1—C12	1.817 (5)
C7—C5—C4	123.4 (3)	C5—C7—S1	121.2 (3)
C7—C5—C6	120.8 (3)	C8—C7—S1	116.8 (2)
C4—C5—C6	115.6 (3)	C7—S1—C12	104.1 (2)
C5—C7—C8	122.0 (3)		

The thienyl ring in (3) exhibits twofold rotational disorder about the C7—C8 axis and the two components were restrained during refinement to be geometrically similar. The relative occupancy was refined to 0.681 (5) for the major component. The S atoms in both components were refined with anisotropic displacement parameters; the higher-occupancy C atoms were modelled with independent isotropic displacement parameters, while a common isotropic displacement parameter was refined for the remainder.

For both compounds, data collection: *DIF4* (Stoe & Cie, 1990*a*); cell refinement: *DIF4*; data reduction: *REDU4* (Stoe & Cie, 1990*b*). Program(s) used to solve structures: *SIR92* (Altomare *et al.*, 1994) for (2); *SHELXTL* (Sheldrick, 1994) for (3). Program(s) used to refine structures: *CRYSTALS* (Watkin *et al.*, 1996) for (2); *SHELXL96* (Sheldrick, 1996) for (3). For both compounds, molecular graphics: *SHELXTL*.

The authors thank EPSRC for provision of a four-circle diffractometer and an Earmarked Studentship (KW), and Lonza Ltd for the generous gift of Meldrum's acid.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1192). Services for accessing these data are described at the back of the journal.

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Chasmaconitine 0.5-Methanol Solvate†

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Abstract

The crystal structure of chasmaconitine hemimethanol solvate, $C_{34}H_{47}NO_9.0.5CH_4O$, a C_{19} norditerpenoid alkaloid, isolated from the roots of *Aconitum chasmanthum* Stapf ex Holmes of Pakistani origin, contains discrete molecules separated by normal van der Waals distances. The fused-ring system contains one boat, one half-chair, two envelope and two chair conformations. The molecular dimensions are normal with no interactions between the alkaloid and the disordered solvate molecules; the mean bond distances are C_{sp^3}—N 1.467 (14), C_{sp^3}—C_{sp^3} 1.54 (2), C_{sp^3}—O 1.42 (2), C_{sp^2}—O 1.337 (5) and C=O 1.197 (5) Å.

Comment

Aconitum chasmanathum Stapf ex Holmes is a small herbaceous shrub which grows wild in Kashmir, Hattian and Rescuta Top. It contains a large number of norditerpenoid alkaloids, *e.g.* chasmaconitine and chasmanthinine (Achmatowicz & Marion, 1964), homochasmanine (Achmatowicz & Marion, 1965), indaconitine (Miana *et al.*, 1971) and chasmanine (Pelletier *et al.*, 1984). The pharmacological properties of the diterpenoid alkaloids which include the control and induction of cardiac arrhythmia, effects on smooth and skeletal muscles, central nervous activity and analgesia, have been reviewed (Benn & Jacyno, 1983; Pelletier & Page, 1986; Amiya

† Alternative name: (1α,6α,14α,16β)-20-ethyl-13-hydroxy-1,6,16-trimethoxy-4-(methoxyethyl)aconitane-8,14-diyl 8-acetate 14-benzoate 0.5-methanol solvate.

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The Effect of 3-Substitution on the Structures of Pyrrole-2-carbaldehydes

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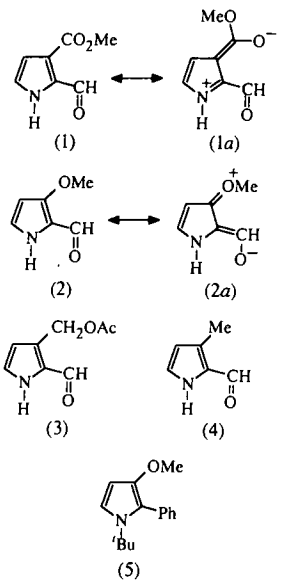
Abstract

In the title compounds, methyl 2-formylpyrrole-3-carboxylate, $C_7H_7NO_3$, and 3-methoxypyrrole-2-carbaldehyde, $C_6H_7NO_2$, the pyrrole rings show little distortion ascribable to the electronic properties of the substituents, whether they are electron donating or electron withdrawing.

Comment

The electronic properties of substituents on unsaturated systems is often found to influence geometry (*e.g.* Blake *et al.*, 1996). We now report the crystal structures of two pyrrole-2-carbaldehydes, one substituted in the 3-position by a strongly electron-withdrawing methoxycarbonyl group, (1), the other similarly substituted with an electron-donating methoxy group, (2), in which the substituents have minimal effect on the structural parameters of the pyrrole ring. Two 3-substituted pyrrole-2-carbaldehydes have been reported previously [(3): Blake *et al.*, 1995; (4): Smith *et al.*, 1985], although (2) is only the third example of a 3-methoxypyrrole to have been structurally characterized (Hunter *et al.*, 1991; Boger & Baldino, 1993).



The aldehyde group is *s-Z* with respect to the N atom of the pyrrole in both (1) and (2), at least in part due to the presence of intermolecular hydrogen bonding. The methoxy substituent at C3 and the methyl ester group are both twisted away from the aldehyde function. Both (1) and (2) are planar; maximum deviations are 0.101 Å for O11 in (1) and 0.046 Å for C9 in (2).

The bond lengths in compounds (1)–(3) are compared in Table 1 and surprisingly there is no significant difference between corresponding bonds in the pyrrole rings, with the exception of N1—C2. Here, the distance increases as a function of the substituent in the order CO_2Me [(1), 1.365 (3) Å] < CH_2OAc [(3), 1.377 (4) Å] < OMe [(2), 1.383 (3) Å]. This is consistent with delocalization of the N-atom lone pair into the ester (1*a*). There is a corresponding decrease in the C2—C(aldehyde) bond lengths [1.444 (3), 1.433 (4) and 1.423 (3) Å in (1), (3) and (2), respectively], consistent with delocalization of the methoxy-based lone pair into the aldehyde function (2*a*). In agreement with this, the C3—O8 bond in (2), at 1.348 (3) Å, is significantly shortened in comparison with the model methoxypyrrole (5), where the corresponding bond length is 1.383 (4) Å.

There are no significant differences in the endocyclic bond angles in (1)–(3). The exocyclic bond angles C2—C3—*X* [*X* = CO_2Me in (1), OMe in (2) and CH_2OAc in (3)] increase in the order (2) < (1) < (3) (see Table 1), in accord with the steric bulk of *X*.

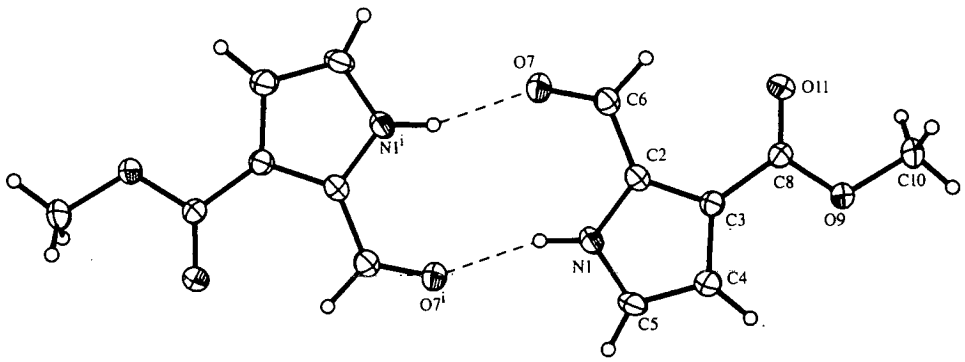


Fig. 1. View of (1) showing the formation of a hydrogen-bonded dimer in the solid state. Distance O7···N1^{i} is 2.842 (3) Å, where (i) is $2-x, -1-y, 2-z$. Ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

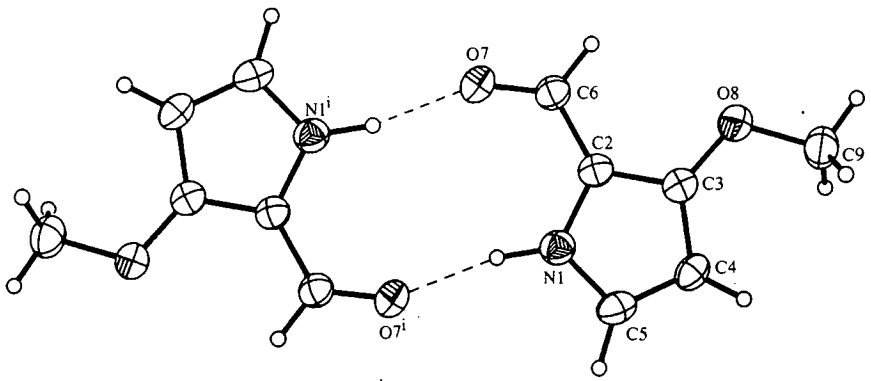


Fig. 2. View of (2) showing the formation of a hydrogen-bonded dimer in the solid state. Distance O7···N1^{i} is 2.797 (3) Å, where (i) is $2-x, 1-y, 2-z$. Ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Packing in the crystal structures of (1) and (2) is characterized by the formation of hydrogen-bonded dimers *via* N—H···O=C interactions. In terms of Etter's graph-set formalism (Etter, 1990), this interaction can be described as an $R_2^2(10)$ system and is consistent with the formation of hydrogen bonds between the most effective donor and acceptor sites.

Experimental

Compounds (1) and (2) were obtained by photochemical ring contraction of the appropriate 4-substituted pyridine-*N*-oxide in aqueous copper(II) sulfate solution (Bisagni *et al.*, 1968; Bellamy *et al.*, 1975). Crystals of (1) and (2) were grown from toluene and chloroform, respectively.

Compound (1)

Crystal data

$C_7H_7NO_3$
M_r = 153.14
Triclinic
$P\bar{1}$
a = 5.6240 (11) Å
b = 7.765 (2) Å
c = 8.569 (2) Å
α = 73.85 (3)°
β = 83.62 (3)°
γ = 88.93 (3)°
V = 357.19 (12) Å^3
Z = 2
D_x = 1.424 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 12.5–16.0°
μ = 0.113 mm^{-1}
T = 150.0 (2) K
Block
0.43 × 0.39 × 0.12 mm
Colourless

Data collection

Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device (Cosier & Glazer, 1986)
ω–2θ scans
Absorption correction: none

976 reflections with $I > 2\sigma(I)$
R_{int} = 0.059
θ_{max} = 25.06°
h = −6 → 6
k = −8 → 9
l = 0 → 10

1271 measured reflections
1264 independent reflections

3 standard reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.046$
$wR(F^2) = 0.129$
$S = 1.054$
1259 reflections
121 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0779P)^2 + 0.0235P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = -0.002$
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.037 (14)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Compound (2)

Crystal data

$C_6H_7NO_2$
$M_r = 125.13$
Monoclinic
$P2_1/c$
$a = 6.9093$ (9) Å
$b = 12.380$ (2) Å
$c = 7.3256$ (11) Å
$\beta = 107.781$ (10)°
$V = 596.7$ (2) Å^3
$Z = 4$
$D_x = 1.393$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 40 reflections
$\theta = 20$–22°
$\mu = 0.888$ mm^{-1}
$T = 220.0$ (2) K
Needle
0.51 × 0.12 × 0.12 mm
Colourless

Data collection

Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device (Cosier & Glazer, 1986)
ω–θ scans
Absorption correction: none
2891 measured reflections
887 independent reflections

689 reflections with $I > 2\sigma(I)$
$R_{int} = 0.075$
$\theta_{max} = 60.16°$
$h = -7 \rightarrow 7$
$k = -13 \rightarrow 13$
$l = -7 \rightarrow 8$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.103$
$S = 1.097$
887 reflections
111 parameters
All H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0572P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.25$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.023 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Comparison of bond lengths (Å) and angles (°) for compounds (1), (2) and (3)*

	(1)	(2)	(3)[a]
N1—C2	1.365 (3)	1.383 (3)	1.377 (4)
C2—C3	1.401 (3)	1.393 (3)	1.389 (4)
C3—C4	1.405 (3)	1.400 (3)	1.402 (4)
C4—C5	1.374 (3)	1.371 (4)	1.370 (5)
N1—C5	1.352 (3)	1.352 (3)	1.351 (4)
C2—C6	1.444 (3)	1.423 (3)	1.433 (4)
C6—O7	1.226 (3)	1.223 (3)	1.225 (4)
C3—C8/O8	1.466 (3)	1.348 (3)	1.502 (4)
C2—N1—C5	110.0 (2)	108.7 (2)	109.0 (3)
N1—C2—C6	121.6 (2)	123.7 (2)	121.9 (3)
C3—C2—C6	131.5 (2)	129.4 (2)	130.6 (3)
N1—C2—C3	106.9 (2)	106.8 (2)	107.4 (3)
C2—C3—C8/O8	125.2 (2)	122.2 (2)	127.1 (3)
C4—C3—C8/O8	127.5 (2)	129.7 (2)	125.7 (3)
C2—C3—C4	107.3 (2)	108.1 (2)	107.2 (3)
C3—C4—C5	107.1 (2)	106.5 (2)	107.3 (3)
N1—C5—C4	108.7 (2)	109.9 (2)	109.1 (3)

Note: (*a*) the numbering scheme has been changed slightly from the original publication to be consistent with those of (1) and (2).

For (1), all H atoms were freely refined with isotropic displacement parameters, except those comprising the methyl group at C10, which was treated as a rotating rigid group. For compound (2), the presence of the low-temperature device during data collection limited the maximum value of 2θ to 120°.

For both compounds, data collection: *DIF4* (Stoe & Cie, 1990*a*); cell refinement: *DIF4*; data reduction: *REDU4* (Stoe & Cie, 1990*b*). Program(s) used to solve structures: *SHELXS86* (Sheldrick, 1990) for (1); *SHELXTL* (Sheldrick, 1994) for (2). For both compounds, program(s) used to refine structures: *SHELXTL*; molecular graphics: *SHELXTL*.

We thank EPSCR for provision of a four-circle diffractometer and an Earmarked Studentship (KW). We are also grateful to Glaxo–Wellcome for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1194). Services for accessing these data are described at the back of the journal.

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